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Case report

Concurrent metastatic ovarian adenocarcinoma of endocervical adenocarcinoma in situ: A case report emphasizing pathologic diagnostic key points and clinical progress

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1. Introduction

Adenocarcinoma in situ (AIS) of the uterine cervix is an intraepithelial lesion containing malignant glandular epithelium. Without proper treatment, it has the potential to progress to invasive adenocarcinoma (Östör, 2000). General data and information regarding in situ lesions of the cervical epithelium have mostly been about squamous epithelial lesions, which does not fully explain its glandular counterpart. For instance, an increase in the diagnosis of in situ squamous cell carcinoma has resulted in a decreased incidence of invasive squamous cervical cancer; however, the growing incidence of cervical AIS (cAIS) has been unable to do so for cervical adenocarcinoma (Teoh et al., 2020). By definition, in situ lesions preclude metastatic or recurrent lesions; however, there have been case reports of recurrent invasive adenocarcinoma originating from cAIS (Ronnett et al., 2008; Chang et al., 2010; Horn et al., 2019; Turashvili et al., 2015).

Such previous reports are rare and most reports feature recurrent lesions after cAIS treatment, with the time interval between diagnoses varying from several months to several years (Ronnett et al., 2008; Chang et al., 2010; Horn et al., 2019; Turashvili et al., 2015; Kim et al., 2019). Only one case has been reported, with concurrent ovarian involvement as an incidental finding during hysterectomy for cAIS.

In the current report, we present a rare case of a phenotypically primary ovarian cancer patient presenting with large mucinous ascites whose pathology report presented metastatic ovarian adenocarcinoma originating from cAIS. Due to limited diagnostic evidence, confirmative pathologic decisions have been deterred. With evidence for postoperative adjuvant therapy even more scarce, our gynecologic oncology team decided to determine her clinical stage prior to proceeding with empirical treatment. As far as we know, this is the first case reporting concurrent metastatic ovarian adenocarcinoma originating from cAIS.

2. Case report

A 50-year-old woman presented to the emergency room with abdominal distension accompanied by abdominal pain in September 2018. Abdominal and pelvic computed tomography revealed a large amount of ascites and an ovarian cystic mass approximately 17 cm in diameter, and radiologists reported primary ovarian malignancy (Fig. 1). On laboratory testing, level of some tumor markers were not remarkable; theses included carcinoembryonic antigen (CEA) 1.5 ng/mL and cancer antigen (CA) 19–9 19.1 U/mL. However, CA 125 level was 108.1 U/mL.. The patient had no significant medicosurgical or gynecologic history, and the preoperative Pap smear tested negative for malignancy. She underwent esophagogastroduodenoscopy (EGD) and colonoscopy to exclude the presence of a mucinous tumor originating from the gastrointestinal tract; the finding were unremarkable. She underwent primary debulking surgery – total abdominal hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection with *para*-aortic lymph node dissection and appendectomy. During the operation, a left cystic ovarian mass with a massive amount of mucinous ascites was noted. No gross lesion of the cervix was noted upon intraoperative examination of the extracted uterus.

Pathological examination demonstrated endocervical AIS, which continued to the endometrium of the uterus corpus and the left fallopian tubal surface without skip lesions. Adenocarcinoma with capsular involvement was noted in the left ovary. Immunohistochemistry showed diffuse strong positivity for p16 in both the cervix and ovaries. Human papilloma virus (HPV) genotyping was performed in the cervix and ovary, and HPV type 18 was found in both specimens. Tumor cells were

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not found in the serosa of the appendix, and cytological examination of the mucinous ascites demonstrated the absence of tumor; in addition, pathological examination confirmed the absence of lymph node metastases. Based on these findings, a permanent pathologic diagnosis of metastatic ovarian adenocarcinoma originating from endocervical AIS was made (Fig. 2).

Upon final diagnosis, the patient was considered to have stage IV disease of uterine cervical malignancy, and received six cycles of post-operative adjuvant chemotherapy (POAC) using paclitaxel and carboplatin. Notably, she experienced a massive pulmonary embolism after the first chemotherapy cycle; hence, appropriate anticoagulation therapy was administered. The patient is undergoing regular follow-ups; 23 months after the last chemotherapy, she is in disease-free status.

3. Discussion

Carcinoma in situ refers to lesions with abnormally increased cellular growth that are restricted to the epithelium. The lack of invasiveness is a key feature of carcinoma in situ lesions; hence, they cannot have distant metastatic lesions or recurrence. Despite its definition, there have been few reports of in situ neoplasms recurring after treatment, with varying prognoses. For breast cancer, Roses et al. reported distant metastases affected after treating ductal carcinoma in situ (DCIS) (Roses et al., 2011). Based on their case series report, 56% of the patients with distant metastatic recurrence after an initial diagnosis of DCIS died. Thus, they postulated that distant metastatic recurrence after DCIS may have a poor prognosis. You et al. also presented a case of bone and sigmoid colon metastases after DCIS treatment (You et al., 2019). They reported that the patient had multiple metastases during post-surgical adjuvant endocrine and targeted therapy.

For gynecologic cancers, prognoses differ in the limited number of case reports. We found that a more favorable outcome is reported after treatment of the metastatic lesions affected by cAIS; however, due to their rarity, we advise close follow-ups during and after treatment for the possibility of poor prognosis similar to DCIS. According to previous case reports, no fatal outcome has been observed and nearly all patients had been disease-free until the pathology reports were made (Kim et al., 2019; Ronnett et al., 2008; Chang et al., 2010; Horn et al., 2019). Based on our review, only one patient was reported to continue maintenance therapy with bevacizumab due to concurrent lung metastases (Horn et al., 2019). In our case, the patient experienced massive pulmonary thromboembolism after the first cycle of adjuvant chemotherapy. Although she desired to stop anticoagulant therapy after the post-operative adjuvant chemotherapy, she was on prophylactic treatment due to a high risk of thromboembolic recurrence.

As mentioned, there are only a handful of case reports on metastatic ovarian carcinoma originating from cAIS (Kim et al., 2019; Ronnett et al., 2008; Chang et al., 2010; Horn et al., 2019). Among them, there was only one case with concurrent ovarian involvement (Chang et al., 2010), which was an incidental finding during simple hysterectomy for cAIS. Thus, as far as we know, this is the first case report presenting phenotypically primary advanced ovarian cancer with no prior history of cervical lesion that was later revealed as metastatic lesion from cAIS. As the ovary is an uncommon metastatic site for uterine cervical carcinoma, concurrent presentation results in difficulty in discerning the lesions as double primaries or primary of one with metastasis of the other. Due to the distinct lack of cases reporting the simultaneous ovarian malignancy involvement of cAIS, diagnosis can be especially challenging. Therefore, our team, comprised of gynecologic oncologists and pathologists, concluded that some diagnostic key points need to be shared.

In this case, we determined that p16 immunohistochemistry revealed an HPV-related tumor, and PCR testing for HPV DNA provided confirmative information to discern primary tumor lesions that cause metastases (Horn et al., 2019; Elishaev et al., 2005; Vang et al., 2007). Similar to its invasive counterpart, in situ lesions of the uterine cervix are mostly affected by HPV (Teoh et al., 2020). In our case, strong diffuse immunopositivity for p16 from the ovaries was noted. Moreover, the positive result for HPV 18 PCR was a solid supporting factor in distinguishing ovarian metastasis from primary AIS.

The selection of platinum was challenging owing to the limited availability of reported information regarding such patients. Although the paclitaxcel/cisplatin combination was preferred for platinum naive patients, the paclitaxcel/carboplatin combination was not inferior, as suggested by the JCOG 0505 trial (Kitagawa et al., 2015). Moreover, only approximately 15% patients in the JCOG 0505 trial had adenocarcinoma of the uterine cervix; this may imply that cisplatin is preferable for squamous carcinoma of the cervix. In this case, the patient only had ovarian invasion of adenocarcinoma while the cervix of AIS. Thus, we finally selected carboplatin, which is the more preferred platinum agent in ovarian adenocarcinoma.

In summary, we present a rare case report of concurrent metastatic

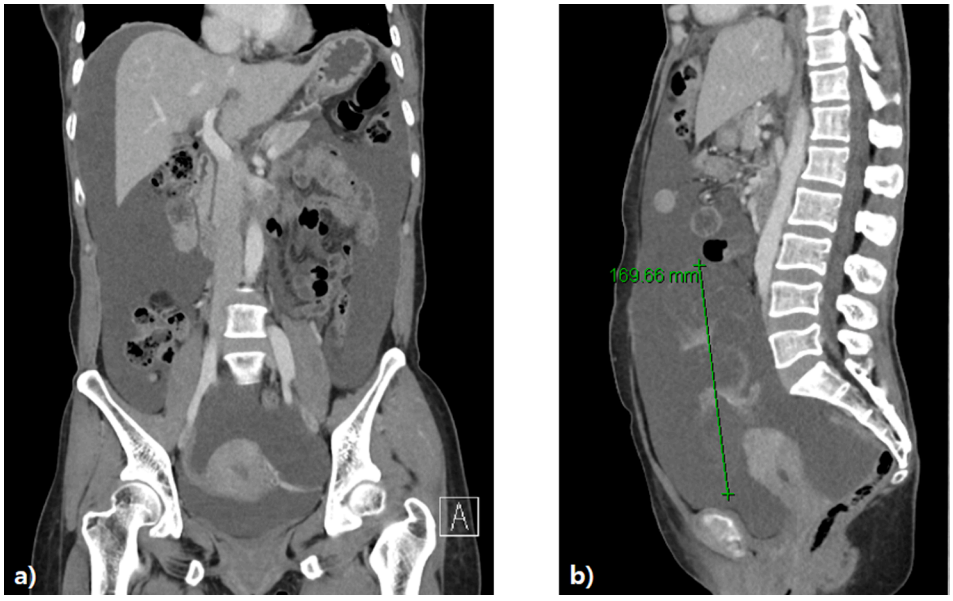

Fig. 1. Initial CT scan revealed large amount of ascites (a), and about an approximately 17 cm cm-sized multi-septated cystic left ovarian mass (b).

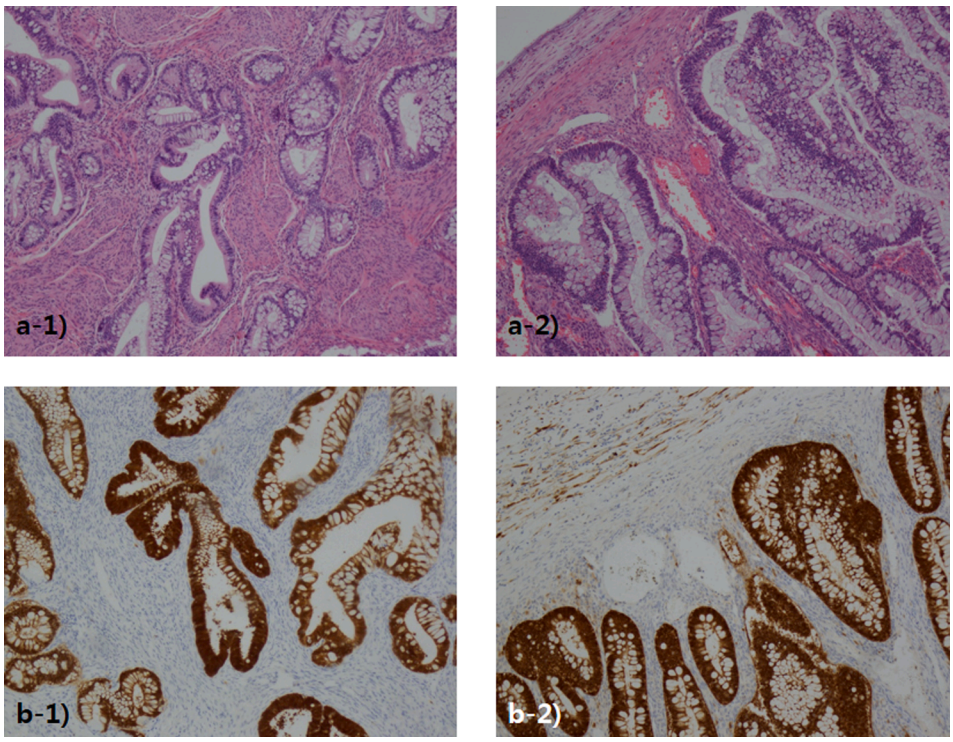

Fig. 2. a-1) The Uterine uterine cervix shows a well well-formed gland composed of pseudostratified columnar epithelium. Invasive growth is not found. (H-E, ×100) a-2) The ovary shows complex glands with cytologic atypia and confluent growth. (H-E, ×100) b-1) p16 Immunohistochemistry for p16 on the cervix reveals diffuse and strong positivity. (×100) b-2) p16 Immunohistochemistry for p16 on the ovary reveals diffuse and strong positivity. (×100).

ovarian carcinoma originating from cAIS. The few case reports of this diagnosis mainly discussed pathology and had limited information for clinicians. In this case, both clinicians and pathologists should be aware of metastatic lesions from cAIS despite the contradiction of such conditions. P16 immunohistostaining and HPV test of surgical specimens may aid in the diagnosis of this rare condition; once diagnosed, POAC might need to be administered and close follow-ups for possible adverse events is advised.

In this case, the patient was initially considered to have advanced stage disease and underwent serious neoplastic side effects; however, her oncologic outcome became favorable after vigorous surgery and adjuvant chemotherapy. Considering its rarity, more case reports are needed to establish treatment plans, a prognosis, and pathologic diagnostic key points regarding the ovarian involvement of endocervical AIS. Furthermore, gynecologists treating cAIS patients should be aware of the possibility of ovarian involvement and consider the recommendation of regular ultrasound follow-ups.

CRediT authorship contribution statement

In Ok Lee: Conceptualization, Methodology, Investigation, Writing - original draft. **Yee Jung Kim:** Conceptualization, Visualization, Investigation. **Hanna Moon:** Writing - review & editing. **Jae Eun Chung:** Conceptualization, Supervision, Validation.

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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