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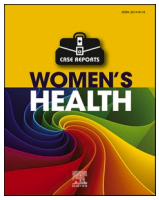

Isolated tubal metastasis from an incidental HPV-associated endocervical adenocarcinoma presented as an adnexal mass: A case report

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ABSTRACT

Tubal metastasis from endocervical adenocarcinoma is uncommon and is discovered as an incidental finding on routine sampling of fallopian tubes. In this paper, we present the case of an 81-year-old woman who presented with an adnexal mass during investigations of postmenopausal bleeding. Hysterectomy and bilateral salpingo-oophorectomy with excision of the left adnexal mass were performed, which led to the diagnosis of an incidental HPV-associated endocervical adenocarcinoma with secondary, macroscopic tubal involvement. The patient received adjuvant pelvic radiotherapy and remained well after three months of follow-up, with no evidence of recurrence. Only a few cases of endocervical adenocarcinoma with tubal metastasis have been reported in the literature, which are commonly associated with ovarian, uterine corpus, and/or parametrial tissue involvement. To date, there are only two reported cases of isolated tubal metastasis, and in both cases, tubal involvement was discovered microscopically. Data on the impact of secondary tubal involvement on patient outcomes are limited.

1. Introduction

Cervical cancer is considered the fourth most common cancer in women worldwide, according to a report from the International Agency for Research on Cancer published in 2021 [1]. It comprises 6.5% of new cancer cases, and cervical cancer is one of the most prevalent cancers in women aged under 45 years in 185 countries [1]. The incidence of cervical carcinoma has increased to 10–25% in developed countries [2,3].

The typical routes of spread for cervical cancer are direct invasion to the parametria and vagina, lymphogenic spread to the pelvic or para-aortic lymph nodes and, less frequently, hematogenous spread to the liver and lungs. While spread to the uterine corpus is not uncommon in large-volume cervical cancers, metastatic spread to the fallopian tubes and ovaries is less well known [4]. Isolated tubal metastasis is exceptionally rare, as most tubal metastases are accompanied by endometrial, ovarian, and/or parametrial tissue involvement. Moreover, most reported cases of cervical carcinoma with secondary tubal involvement, whether isolated or not, were microscopic findings and the tubes were grossly unremarkable [5].

In this report, we present a case of isolated tubal metastasis from human papilloma virus (HPV)-associated endocervical adenocarcinoma in an 81-year-old woman who presented with an adnexal mass.

2. Case Presentation

An 81-year-old Caucasian woman presented with a 2-week history of postmenopausal vaginal bleeding and clear discharge, with no other gynecological or general symptoms. The patient had a history of combined hormone replacement therapy from the age of 54 to 59 years and anterior repair of vaginal prolapse at the age of 80 years, but no significant medical history. The patient had a normal smear history, and her last smear was performed at the age of 65 years, as per the National Cervical Cancer Screening Guidelines in the United Kingdom. Clinical examination, including speculum examination, showed normal vulva, vagina, and cervix, while rectovaginal examination revealed a pouch of Douglas mass on palpation. Transvaginal ultrasonography showed a normal endometrial thickness of 2 mm and a solid mass with increased vascularity in the left side of the pelvis. The CA125 serum tumor marker test was normal at 14.0 units/ml. Pelvic magnetic resonance imaging (MRI) demonstrated a 64 mm mixed solid-cystic adnexal mass with a moderate amount of fluid and a subcapsular liver lesion. The subsequent

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PET-CT scan showed no increased uptake in the liver lesion and revealed a simple liver cyst. A multidisciplinary tumor board meeting recommended that the patient undergo a staging laparotomy. A staging operation, including total hysterectomy with bilateral salpingo-oophorectomy, infracolic omentectomy, and peritoneal biopsies, was performed, and the postoperative period was uneventful.

Gross inspection of the surgical specimen revealed that the left adnexal mass consisted of a dilated tube with a blunt fimbrial end. The center of the tube showed a whitish firm mass surrounded by a thin flaccid cyst. The mass measured 50 mm in the maximum dimension. The central part of the tube was filled with necrotic white tissue, which filled the lumen and extended into the serosa. The mass had a more friable papillary outline in the proximal part of the tube. A small atrophic ovary was observed at the edge of the tube. The hysterectomy specimen revealed a cervix with a small cyst. Macroscopic abnormalities were not observed. The endometrial lining, right fallopian tube and ovaries were within normal limits. Samples from the mesenteric scar tissue, paracolic peritoneum and omentum consisted of fragments of fat tissue with no abnormalities observed or felt.

On microscopy, the central part of the left tube, where the mass was noted macroscopically, showed adenocarcinoma with a prominent papillary architecture. The carcinoma was centered on the wall of the tube and infiltrated into the tubal lamina propria and muscularis. The carcinoma was composed of atypical columnar cells with pseudostratified nuclei, numerous supranuclear mitotic figures, and scattered apoptotic cells (Fig. 1). No squamous metaplasia was observed. No psammomatous calcifications were noted. The adjacent normal-appearing tube showed no evidence of serous tubal intra-epithelial carcinoma (STIC). Several foci of lymphovascular invasion were seen. The right tube and both ovaries were normal. The cervix showed a small focus of HPV-associated adenocarcinoma arising from a background of adenocarcinoma in situ (AIS). The tumor cells were morphologically similar to those observed in the left adnexal mass. The carcinoma measured 1.2 mm in maximum depth. All the resection margins were clear. No definite lymphovascular invasion was seen in the cervix. The cervical carcinoma featured fairly well-demarcated neoplastic growth associated with focal destructive stromal invasion accompanied by desmoplastic stromal reaction and was labelled as Silva pattern B (Fig. 2).

The endometrium was widly sampled and showed benign endometrial polyps in the background of inactive endometrium. The vagina, peritoneal samples and omentum were tumor-free. Immunohistochemistry showed that the carcinoma in the tube and cervix had a similar immunoprofile, and both showed block staining for p16 (Fig. 1D & 2D). Both were positive for CK7 and negative for CK20, CDX2, SATB1, estrogen (ER) and progesterone (PR) receptors. Based on these findings, the diagnosis of well-differentiated, HPV-associated endocervical adenocarcinoma with left tubal metastasis was confirmed.

The multidisciplinary cancer team concluded that the cervical cancer was FIGO stage IA1, as tubal involvement was not included in the International Federation of Gynecology and Obstetrics staging classification. However, considering the tubal spread, the patient was referred to a clinical oncologist for external beam radiotherapy. The patient remained well with no evidence of recurrence or distant metastasis after three months of follow-up.

3. Discussion

Cervical cancer is the fourth most common cause of cancer-related death in women globally, representing 7.7% of 4.4 million deaths [1]. Even though the number of new cases of cervical cancer has been declining steadily over the past decades, this is due to a decrease in the number of cervical squamous cell carcinomas. In the meantime, there has been an increase in the incidence of cervical adenocarcinoma. This may be related to various factors, including obesity, nulliparity, and oral contraceptive use. One possible contributing factor is the deep location of glandular lesions in the cervical canal, which can lead to difficulties in cytological and colposcopic recognition. Moreover, the cytology-based

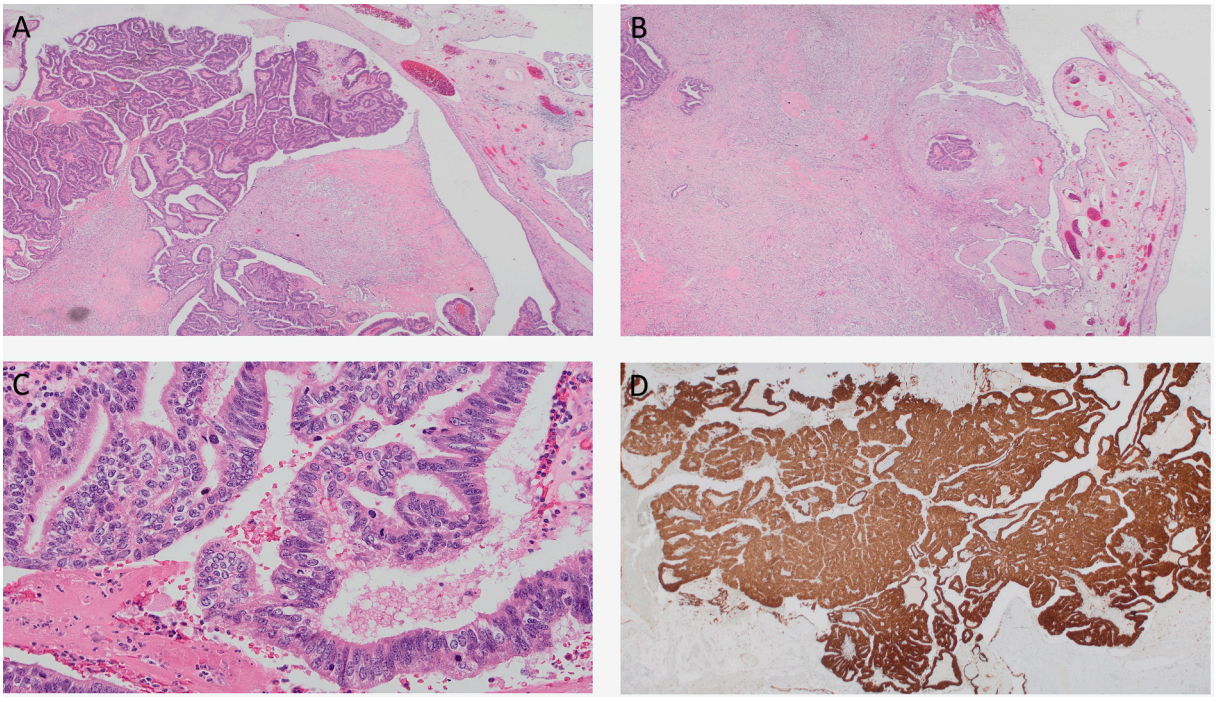

Fig. 1. Microscopic appearances of adnexal mass.
A, B: High-power view showing an adenocarcinoma with prominent papillary architecture. Note the adjacent normal fallopian tube in fig. B.
C: Lower-power view showing the atypical columnar epithelium with pseudostratified, hyperchromatic and enlarged nuclei along with frequent supranuclear mitotic figs.
D: The carcinoma shows block positive staining for p16.

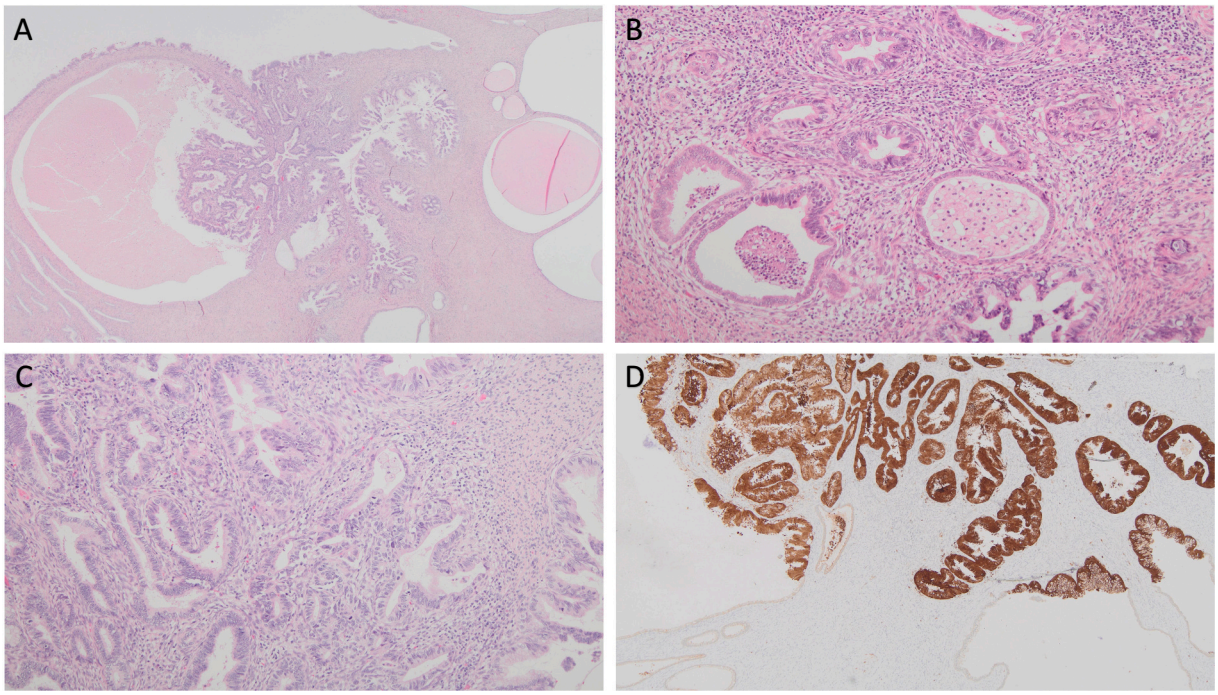

Fig. 2. Microscopic appearances of the HPV-associated cervical carcinoma.
A, B: High- and low-power views showing a small well-demarcated adenocarcinoma arising from a background of adenocarcinoma in situ (AIS). The carcinoma is arranged mostly in the form of packed glands with focal stromal invasion accompanied by a desmoplastic reaction in Fig. B; hence, Silva Pattern B.
C: The lining cells show features similar to those in the tube, with the characteristic numerous supranuclear mitotic figures and scattered apoptotic bodies.
D: The carcinoma shows block positive staining for p16.

screening is not considered an effective tool in detecting HPV-independent adenocarcinomas. Given that these carcinomas are not recognized by HPV-based screening, they are usually present at advanced stages [2,3].

Metastasis of the upper female genital tract by cervical cancer is uncommon. Most cases reported in the literature are metastatic squamous cell carcinomas [4]. There are 32 reported cases of endocervical adenocarcinoma that were investigated and confirmed to have tubal metastasis with involvement of other parts of the female genital system, such as the ovary, *endo*-myometrium and parametrial tissue (Table 1). These cases included 12 HPV-associated adenocarcinomas, 17 HPV-independent adenocarcinomas (gastric type), two adenocarcinomas (not otherwise specified) and one neuroendocrine carcinoma [4–11]. Of these malignancies, only two showed isolated tubal metastasis. The first case was an HPV-associated endocervical adenocarcinoma reported by Reyes et al. in 2016 and the second was a moderately differentiated endocervical adenocarcinoma, not otherwise specified, as reported by Manoharan et al. in 2018 [4,9]. In both cases, tubal metastasis was a microscopic finding with no gross abnormalities.

In our case, the cervical carcinoma was incidentally discovered, and the main presentation was an adnexal mass constituting the fallopian tube distended by metastatic endocervical cancer. This observation is distinct from all of the published cases in the literature, where cervical cancer was the primary diagnosis and tubal metastasis was discovered incidentally. For instance, Lee et al. investigated four out of five cases of endocervical adenocarcinoma (two HPV-associated and two HPV-independent, gastric type); in all cases, tubal metastasis was noted microscopically in the form of intra-epithelial deposits confined to the tubal mucosa [5].

Isolated tubal metastasis from FIGO stage IA1 endocervical adenocarcinoma, that is, diagnosed only by microscopy, can mimic primary tubal carcinoma, such as high-grade serous carcinoma (HGSC), endometrioid carcinoma, and metastasis from primary gastrointestinal origin. Morphologically, HGSC usually exhibit papillary tufts and slit-like glandular spaces lined by highly atypical tumor cells with marked nuclear pleomorphism and frequent mitotic figures. It most commonly arises from STIC, which is largely seen in the fimbria of the tube [12]. Endometrioid carcinoma of the tube is mostly composed of solid proliferation of small, closely packed glands with or without squamous differentiation [13]. Metastatic colorectal carcinoma usually exhibits cribriform growth or individual glands, showing a characteristic garland pattern of dirty necrosis. It is typically lined by mildly atypical pseudostratified nuclei and usually shows areas with mucinous/intestinal-type epithelium [14]. Moreover, the presence of nuclear atypia that is not proportional to architectural features can be helpful in raising the suspicion of metastatic carcinoma. HPV-associated endocervical adenocarcinoma shows numerous apically situated mitotic figures and basally situated apoptotic debris appreciable at scanning magnification [4]. Endocervical carcinomas with mucinous components, including mucinous and gastric-type adenocarcinomas, show intra-cytoplasmic mucin and may have goblet cells, neither of which is observed in HGSC [5,11]. Finally, the morphological and immunohistochemical similarities between primary and metastatic tumors support the diagnosis of metastatic involvement of the tube.

Immunohistochemistry is a useful tool for establishing an accurate diagnosis. Metastatic endocervical carcinoma is expected to show block staining for p16 and positivity for HPV RNA in situ hybridization. It is also positive for PAX8 and CK7, but negative for WT1, ER and PR. Most cases of HGSC are positive for WT1, ER and shows an aberrant pattern of staining for p53 and block staining for p16, but they should be negative for HPV testing [4,11]. In well-differentiated endometrioid carcinoma, ER is almost always positive, while WT1 is expected to be negative. p53 usually shows an aberrant pattern of staining, while p16 shows non-block staining. Metastatic carcinoma of colorectal origin is positive for CK20, CDX2, and SATB1, while negative for CK7 [14]. The correlation between the morphology and immunoprofile of cervical carcinoma in such cases can be helpful to avoid misinterpretation.

The pathogenesis of tumor spread within the gynecological system

Table 1
Reported cases of cervical adenocarcinoma with secondary tubal involvement.

Year	Author	Age	Type of Adenocarcinoma	FIGO stage	Laterality of tube	Involvement of other site in female reproductive system
1997	Wu et al. [6] case 7	50	NOS	IB	–	UC, ovary
2016	Deel et al. [7]	50	HPVA with focal mucinous and intestinal differentiation	IB1	R	UC
2016	Reyes et al. [4] case 11	68	HPVA, usual type	IIA2	R	UC
	Reyes et al. case 12	49	HPVA, usual type	IIA2	R	UC, ovary
	Reyes et al. case 15	45	HPVA, usual type	IB1	L	UC
	Reyes et al. case 16	40	HPVA, usual type	IIB	R	ovary
	Reyes et al. case 17	48	HPVA, usual type	IIB	BL	UC
	Reyes et al. case 18	44	HPVA, usual type	IIA2	R	UC, both ovaries
	Reyes et al. case 19	41	HPVA, usual type	IVB	L	UC, both ovaries
	Reyes et al. case 20	37	HPVA, usual type	IB1	L	–
2018	Rajendran et al. [8] case 1	44	HPVI, gastric-type	–	L	UC, both ovaries
	Rajendran et al. case 2	61	HPVI, gastric-type	–	L	UC, ovary, paracervical/parametrial tissue
	Rajendran et al. case 3	68	HPVI, gastric-type	–	BL	UC, both ovaries
	Rajendran et al. case 4	58	HPVI, gastric-type	–	BL	UC, ovary, paracervical/parametrial tissue
	Rajendran et al. case 5	64	HPVI, gastric-type	–	R	UC, ovary paracervical/parametrial tissue
	Rajendran et al. case 6	48	HPVI, gastric-type	–	BL	UC, vagina (on imaging), both ovaries
	Rajendran et al. case 7	51	HPVI, gastric-type	–	BL	Ovary, paracervical/parametrial tissue
2018	Manoharan et al. [9]	57	NOS	–	R	
2020	Abozina et al. [10]	55	HPVA, usual type	IA1	L	Both ovaries
2021	Lee et al. [5] case 1	61	HPVA, usual type	IIIC	L	UC, vagina, parametrial tissue
	Lee et al. case 2	64	HPVA, mucinous type	IIIC	BL	UC, parametrial tissue
	Lee et al. case 3	42	HPVI, gastric type	IIB	R	Parametrial tissue
	Lee et al. case 4	54	HPVI, gastric type	IIB	BL	UC, vagina, parametrial tissue
	Lee et al. case 5	51	NEC	IVB	R	UC, vagina, parametrial tissue
2022	Lu et al. [11] case 1	46	HPVI, gastric type	IIB	BL	UC, ovary, parametrial tissue
	Lu et al. case 2	47	HPVI, gastric type	IB2	R	UC, both ovaries
	Lu et al. case 3	36	HPVI, gastric type	IIIC1	R	UC, both ovaries
	Lu et al. case 4	42	HPVI, gastric type	IIIC2	BL	UC, both ovaries, parametrial tissue
	Lu et al. case 5	62	HPVI, gastric type	IIB	BL	UC, Both ovaries
	Lu et al. case 6	56	HPVI, gastric type	IVA	R	UC, Both ovaries
	Lu et al. case 10	38	HPVI, gastric type	IIIC1	R	Both ovaries
	Lu et al. case 12	66	HPVI, gastric type	IVA	BL	Both ovaries

HPVA, HPV-associated adenocarcinoma; HPVI, HPV-independent adenocarcinoma; NOS, not otherwise specified; NEC, neuroendocrine carcinoma; R, right; L, left; BL, bilateral; UC, uterine corpus including endometrial and/or myometrial involvement.

has been postulated in other organs. Based on these suggested mechanisms, tubal metastasis might occur through the following pathways: transuterine route via intra-epithelial spread or tumor cell exfoliation, trans-coelomic route or lymphovascular invasion [15]. The transuterine/transtubal route of spread has been observed in early cervical carcinomas with indolent behaviour [7,15]. The trans-coelomic route has been observed in advanced cervical carcinomas with aggressive behaviour [5,15]. Of note, in our case, metastatic carcinoma skipped the uterine corpus, peritoneum, ovaries, and involved the fallopian tube; therefore, the most likely suggested mechanism for metastasis is lymphovascular invasion (LVSI). Interestingly, the cervical cancer in this case showed no LVSI, but tubal involvement did.

The literature has limited data on the effects of tubal involvement on patient prognosis and management as tubal involvement is not included in the International Federation of Gynecology and Obstetrics staging classification for cervical carcinoma. Future studies are warranted to examine the impact of secondary invasion of the upper female genital system by cervical carcinoma on patient outcomes.

4. Conclusion

In summary, we present an unusual case of isolated large tubal metastasis from an incidental primary HPV-associated endocervical adenocarcinoma that presented as an adnexal mass. We also discuss potential histopathological differential diagnoses and possible modes of spread. The clinical impact of isolated tubal metastasis remains unknown.

Contributors

Hessa Aljhdali contributed to drafting the manuscript and undertaking the literature review.

Janos Balega contributed to patient care, acquiring clinical data and revising the article critically for important intellectual content.

Anthony Williams contributed to interpreting the histopathological findings, diagnosis of the patient and revising the article critically for important intellectual content.

Raji Ganesan contributed to the final diagnosis of the patient, conception of the case report, acquiring digital photographs for the histopathology, undertaking the literature review, writing, revising and editing the article, and overall supervision.

All authors approved the final submitted manuscript.

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Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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members of *Case Reports in Women's Health*, who were blinded to the process.

Conflict of interest statement

The authors of this article have no conflicts of interest to declare.

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