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METASTASIS OF CERVICAL CARCINOMA TO THE OVARY: A CASE REPORT

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ABSTRACT:

Background: Human Papillomavirus (HPV) infection is the primary cause of cervical cancer. Although metastases most frequently occur through the lymphatic system to nearby organs, distant metastases, such as to the ovaries, can also arise but are less common. Prompt detection of these metastases is critical for effective treatment.

Case Presentation: We report the case of a 57-year-old female patient with a history of neoplastic disease, histologically and immunohistochemically confirmed as endocervical adenocarcinoma, stage Ib2, with ovarian metastases. The patient's medical history includes bilateral salpingo-oophorectomy, pelvic paraaortic lymphadenectomy, and omentectomy. This study was conducted at Hayatabad Medical Complex, Peshawar, KPK Pakistan.

Clinical Course: One year post-chemotherapy, the patient presented with genital bleeding, right iliac fossa pain, and intestinal constipation. Speculum examination revealed a vegetative lesion of the vaginal fundus. Biopsy identified a well-differentiated adenocarcinoma (Grade 1). Pathological findings indicated villoglandular adenocarcinoma infiltrating the vaginal wall, necessitating a corpectomy which was performed successfully. The patient received subsequent brachytherapy and radiation treatment.

Outcome: Post-treatment colposcopic findings and oncotic cytology were within normal limits. The patient showed no signs of disease recurrence.

Conclusion: Although ovarian metastases from cervical cancer are rare, their possibility must be recognized. Prognostic evaluation should consider clinicopathological factors and imaging tests, including tumour size, lymph node status, and depth of myometrial invasion. Early detection and comprehensive treatment are essential for optimal patient outcomes.

KEYWORDS: Ovaries, Metastasis, Adenocarcinoma, Cervical Cancer, Human Papillomavirus (HPV), Bilateral salpingo-oophorectomy, Pelvis paraaortic lymphadenectomy, Omentectomy Chemotherapy, Colpectomy, Brachytherapy.

INTRODUCTION:

Over 90% of cases of cervical cancer are brought on by an infection with the Human Papillomavirus (HPV). This virus causes the cervical epithelium to spread excessively, which might result in cellular alterations that eventually lead to cancer. Use of contraception, immunosuppression, having several partners, and a personal history of STIs are risk factors. This carcinoma, which ranks as the fourth leading cause of mortality for women in poor nations, is regarded as a public health concern and the most prevalent gynaecological cancer. Approximately 40% of them affect fertile (Casey & Singh, 2020; Honda et al., 2024; Laios et al., 2021; Su, Song, Wu, Fan, & Li, 2024). The WHO estimates that 311,000 people died, and over 570,000 new cases of cervical cancer were detected in 2018. Squamous cell carcinoma (SCC) and adenocarcinoma (ADC) are the most prevalent histological subtypes, accounting for around 75% and 25% of all cervical carcinomas. Because of the tumour's high frequency, early diagnosis is essential for appropriate treatment, which lowers the disease's morbidity and death rate. This condition is asymptomatic for the most part. Vaginal bleeding during sexual activity, dark-coloured discharge, an unpleasant odour, and, in more advanced stages, bleeding and intestinal and urinary tract blockage are among the most prevalent symptoms (Q. Chen, Shen, & Xie, 2020; Gardner et al., 2020; Olmes et al., 2024; M. Wu et al., 2024).

However, women tend to know very little about these symptoms, which makes it challenging to recognize the issue and lets the illness progress to later stages without being detected in its early stages. Moreover, the hypothesis suggests that late treatment seeking and inadequate awareness of the symptoms are connected to the mortality relation associated with cervical cancer. Malignant neoplasms of the cervix are staged by the International Federation of Gynaecology and Obstetrics (FIGO) system, which uses variables from imaging tests, biopsies, physical examinations, proctoscopies, and cytoscopies; pathological staging can also be done in the event of surgery, but it does not alter the clinical staging (Chang et al., 2024; Praja & Perbowo, 2024; Zhang, Zhang, Wang, & Shen, 2022).

According to this system, tumours are categorized into grades I through IV, with progressively more severe subclassifications ranging from carcinoma in situ to carcinoma in situ when cancer spreads to distant locations, including the lungs and bones. Stage I tumours only extend to the cervix, whereas stage II tumours extend past the cervix but do not extend to the pelvic wall or the bottom third of the vagina. Tumours in stage III already impact the pelvic wall and the lower vaginal wall or result in hydronephrosis. Stage IV tumours either have distant metastases or reach the mucosa of the bladder or rectal area (Chandra, Kumari, & Sharma, 2024; Ogimoto et al., 2024; Z. Shi, Yang, & Bian, 2022). However, the World Health Organisation (WHO) recommends that all tumours be examined under a microscope to determine whether the primary tumour is genuine of cervical origin. This is crucial because a clinical diagnosis alone is insufficient. By dividing cancerous cells into distinct morphological forms, such as SCC and ADC, each has its subclassifications and determines if the cancerous cells are differentiated, moderately differentiated, or undifferentiated. Regarding immunohistochemical criteria, samples from primary and secondary malignant tumours of the cervix must be used for immunological testing (Abdelsamia, Mosalem, Gogineni, Gullapalli, & Olomu, 2022; Sugitani et al., 2024; J. Wu et al., 2024). This is because biopsies enable the identification of the tumour's histotypic patterns, which confirms the neoplastic origin. These additional indicators act as shifting differentials for other early malignancies such as different types of endometrial, ovarian, breast, and including neoplasms as well as gastric tumours. Based on the studies and literature, an elevated positive attitude toward CEA in the ADC of the cervix could be verified. In contrast, a positive attitude to p63 antibodies occurs only in SCCs of the same site. Similar results occur when the immunoreactivity of antibodies of CK7, CK20, CDX2, ER, PR, GFCDP-15, E-cadherin, and p16 are compared. Another crucial tool for determining the

presence of endocervical ADC is the PAX antibody (Anjum, Maqsood, Younus, Anjum, & Fatima, 2021; Neil, Li, Hakam, Nucci, & Parra-Herran, 2024; Vias, Saklani, Singh, Thakur, & Sankhyan, 2024). The disease can spread when the tumour penetrates the basal lamina and enters the blood, lymphatic systems, and nearby organs. Most often, lymphatic pathways are used by metastases to spread, and they might reach the para-aortic and pelvic lymph nodes. These are the ten most common places for cervical cancer; the lungs, bones, and liver are affected in about 10% of cases. In FIGO stages IA through IIB, the incidence of ovarian metastasis in ADC of the cervix is 3.61%, while in SCC, it is 1.46%. Additionally, patients with tumors larger than 4 cm and those over 40 are at risk for metastasis because they are frequently uncommon and have a low incidence; metastases from primary cervical tumors can be missed, which makes identification and effective treatment challenging (Li & Zheng, 2024; Otsuka, 2024). From this perspective, the correct diagnosis greatly depends on staging, morphological, and immunohistochemical criteria.

Table 1: Cervical Cancer Overview and Risk Factors

Aspect	Description	References
Primary Cause	Human Papillomavirus (HPV) infection	(Honda et al., 2024; Su et al., 2024)
Pathogenesis	HPV causes excessive spread of cervical epithelium, leading to cellular alterations and cancer	(Honda et al., 2024; Su et al., 2024)
Risk Factors	Contraceptive use, immunosuppression, multiple sexual partners, personal history of STIs	(Honda et al., 2024; Su et al., 2024)
Public Health Concern	The fourth leading cause of mortality for women in poor nations, the most prevalent gynaecological cancer	(Honda et al., 2024; Su et al., 2024)
Impact on Fertile Women	Approximately 40% of cases affect fertile women.	(Honda et al., 2024; Su et al., 2024)
WHO Statistics (2018)	311,000 deaths and over 570,000 new cases of cervical cancer detected	(Olmes et al., 2024; Wu et al., 2024)
Histological Subtypes	Squamous cell carcinoma (75%) and adenocarcinoma (25%)	(Olmes et al., 2024; Wu et al., 2024)
Symptoms	Vaginal bleeding, dark-coloured discharge, unpleasant odour, advanced stages may include bleeding and urinary/intestinal blockage.	(Olmes et al., 2024; Wu et al., 2024)

Table 2: Diagnostic and Staging Criteria

Criteria	Description	References
Staging System	FIGO system, using imaging tests, biopsies, physical exams, proctoscopies, cystoscopies	(Chang et al., 2024; Praja & Perbowo, 2024)
Pathological Staging	Performed in the event of surgery, does not alter clinical staging.	(Chang et al., 2024; Praja & Perbowo, 2024)
Tumor Grades	I to IV, with subclassifications ranging from carcinoma in situ to	(Chandra et al., 2024; Ogimoto et

	distant metastases.	al., 2024)
Histological Examination	WHO recommends microscopic examination to confirm cervical origin.	(Chandra et al., 2024; Ogimoto et al., 2024)
Immunohistochemical Testing	Differentiates between SCC and ADC assesses markers like CEA, p63, CK7, CK20, CDX2, ER, PR, GFCDP-15, E-cadherin, p16, PAX	(Neil et al., 2024; Vias et al., 2024)

Table 3: Metastasis and Treatment

Aspect	Description	References
Metastasis Pathways	Blood, lymphatic systems, nearby organs, commonly lymphatic to para-aortic and pelvic lymph nodes	(Li & Zheng, 2024; Otsuka, 2024)
Common Metastasis Sites	Lungs, bones, liver (10% of cases)	(Li & Zheng, 2024; Otsuka, 2024)
Ovarian Metastasis Incidence	ADC: 3.61%, SCC: 1.46% in FIGO stages IA-IIB	(Li & Zheng, 2024; Otsuka, 2024)
Risk Factors for Metastasis	Tumors >4 cm, patients >40 years	(Li & Zheng, 2024; Otsuka, 2024)
Treatment Options	Surgery, local procedures, fertility preservation in younger patients, follow-up with clinical, cytological, and colposcopic exams	(Chen et al., 2024; Fattorini et al., 2024)

Numerous studies address the risk variables that influence ovarian metastases and recommend the preservation or removal of the ovaries. Nonetheless, the topic is still debatable because there isn't much research that considers all risk factors. Treatment for invasive ADC involves surgery and is done using local procedures. To protect the woman's fertility, it may be possible for younger patients and in certain situations to continue with clinical, cytological, and colposcopic follow-up following the biopsy (J. Chen, Wang, Wu, Hsiao, & Chang, 2024; Fattorini et al., 2024).

CLINICAL CASE:

The 57-year-old woman, G3P3(1C)A0, went through menopause at the age of 53, was on hormone replacement treatment for six months, and complained of severe abdominal discomfort and continuous vaginal bleeding for two years. She had a rounded neck, an external opening in a transverse fissure, and no apparent abnormalities upon speculum inspection. The cervix was thick and nasal, had a closed external orifice, was painless with mobilization, and had an expansion in the right adnexal region upon vaginal inspection. She had a right adnexal mass on transvaginal ultrasonography, and a right pleural effusion was visible on the chest x-ray. It was consequently decided to undertake an exploratory laparotomy alongside the patient (Meloni et al., 2024; Papapanagiotou et al., 2024).

Due to the discovery of foci suggestive of malignant disease during the inventory of the abdominal cavity, a total hysterectomy with bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, and omentectomy was chosen. The results of the immunohistochemistry and anatomopathology revealed a well-differentiated endocervical ADC with stage Ib2, and the ovarian lesion's presence of p16 protein verified that the endocervical ADC had metastasized to the ovary (Table 1 and Figure 1). Adjuvant chemotherapy was then recommended for the patient. She started

having genital bleeding and right iliac fossa pain, along with constipation, a year after she finished chemotherapy (Gashawbeza, Dereje, & Abubeker, 2024; KIKVADZE et al., 2024).
The biopsy of the vegetative lesion in the vaginal cul-de-sac revealed a well-differentiated ADC, nuclear grade 1, which was also shown by the speculum examination. Given the pathological evidence of a villoglandular ADC invading a sample of the vaginal wall, a corpectomy was recommended and carried out. In addition to adjuvant brachytherapy, the patient received radiation. Given the anatomopathological findings of villoglandular ADC infiltrating a sample of the vaginal wall, a corpectomy was recommended and carried out. In addition to adjuvant brachytherapy, the patient received radiation. Following treatment, the patient's colposcopic findings and oncotic cytology were both within normal limits (Macêdo et al., 2024; Song, Li, Wang, & Wang, 2024).

ANTIBODIES	CLONE	OUTCOME
Resulting from the tumour suppressor gene p16 (INK4)	G175–405.	Positive
CEA, or carcinoembryonic antigen,	Poly Clonal	Positive

Table 1*: Results of the patient's immunohistochemical examination.*

DISCUSSIONS & CONCLUUSION:

Compared to SCC, ADC is a less common histopathological subtype of cervical cancer. However, in contrast to the squamous type, the incidence of ADC is rising, as reported by the Federation of Gynaecology and Obstetrics Association. Consequently, for therapy to be effective and lower morbidity and mortality, early diagnosis is required. Endocervical ADC is a diverse illness with various histological subtypes, aetiologies, and clinical manifestations. Roughly 90% of endocervical ADCs are high oncogenic risk HPV-related neoplasms, specifically subtypes 16 and 18. The remaining 10% are not HPV-related, and neither type often spreads to the ovaries (Kashihara et al., 2024; Thakur, Anjum, & Qadri, 2024).
Eighty per cent of ADCs are thought to be of the typical kind and to be p16 positive. Its greater than 12-month-long replication in the surface layers promotes extended infection, an increase in the viral load, and the viral genome integration into the cell.
Findings in the literature indicate that the presence of the p16 protein is a marker for high-risk HPV 1 infection. When distinguishing between primary ovarian tumours and metastatic ADCs related to HPV-related endocervical ADCs that have metastasized to the ovary and other sites that are included in the differential diagnosis of ovarian tumours with mucinous and endometrioid differentiation, this protein's expression is sensitive and specific (Farahani et al., 2024; Rahimi et al., 2024).
Since other markers, like CEA and CA-125, have minimal utility and present sensitivity for ovarian tumours ranging between 80% and 85%, as well as being variable among the developmental stages of tumour ADC, being smaller in the early stage and more significant in the advanced stages, and being present in several primary types of ovarian epithelial tumours, metastatic ADCs from different sites, and even endocervical ADCs, the identification of p16 as a marker of ovarian metastatic endocervical ADC is helpful. An ADC of the usual type is present in the patient's immunohistochemistry panel. Architecturally, this pattern is characterized by various shaped and sized glands, while papillary, cribriform, and solid sections can also be observed. In other words, it can display a range of invasion patterns, from those that in ADC can identify as invasive with ease to those that are very difficult or tough to do so (Dewan, Shrivastav, Shrivastav, & Singhal, 2024; Novikov, Anufriev, & Efremov, 2024).
As a result, the invasive pattern is classified as confluent glandular or cribriform, papillary or villoglandular, infiltrative or destructive (AVG). With a slow course and infrequent lymphatic and/or vascular invasion, AVG is an uncommon subtype of cervical ADC that is differentiated and has a better prognosis than average ADC. It is more common in young women and those who are fertile. Since histology was used to diagnose it, cytological screening cannot identify it. Consequently, it was determined that the diagnosis of ovarian metastatic involvement by

endocervical ADC is supported by the clinical, histological, and immunohistochemical data (Chiu, Lau, Tan, & Huang, 2024; Karamooz, Binsol, Asirvatham, & Pargaonkar, 2024).

Even though ovarian metastases are uncommon, a cohort study showed that individuals with ADC had a greater probability of ovarian metastases from early cervical cancer (0.5% in SCC, 1.7% in ADC). One case had concurrently diagnosed clinically evident cervical and ovarian masses, eleven clinically unsuspicious tumours were diagnosed simultaneously in specimens obtained for ovarian mass evaluation, one case had an occult tumour discovered after ovarian metastases and 29 cases of synchronous and metachronous endocervical and ovarian tumours were analyzed. Of these, 18 cases had invasive cervical tumours (Salman & Covens, 2024).

As per Fan et al., patients with ADC and SCC had a comparatively low incidence of ovarian metastasis, with the former having an almost three-fold greater incidence than the latter.

The patterns of borderline consolidated glandular, cribriform, and vloglandular ovarian tumours are similar to those of well-differentiated carcinomas or atypical proliferative primary ovarian tumours. In research, these patterns were pure in 24 cases and intermingled with lesser infiltrative foci in two instances. Moreover, the ovarian tumours only displayed the classic features of metastases (bilateral and infiltrative) in 3 patients. The ovarian tumours metastasized because all HPV-related cases had paired endocervical and ovarian tumours with the same type of HPV (Bianchi et al., 2024; X. Shi et al., 2024).

The following are risk factors for ovarian metastases: involvement of the pelvic lymph nodes, penetration of the uterine corpus, invasion of the parametrium, giant tumours (greater than 4 cm), and advanced age (over 40 years). Therefore, Ovarian conservation may be prudent and reasonable for young women, but patients with risk factors should take extra measures.

Treatment options for stages IB2 to IIA include radical hysterectomy and bilateral pelvic lymphadenectomy, occasionally in conjunction with radiation therapy. The most typical technique is a combination of chemotherapy and pelvic radiation therapy (Chow & Fabian, 2024).

The National Cancer Institute states that the best available scientific data now supports a combination of radiation therapy and chemotherapy followed by brachytherapy for enormous stages IB2 and IIA (lesions greater than 4 cm), IIB, IIIA, IIIB, and IVA. It was shown in the landmark randomized trial by Landoni that the survival rates for aggressive surgery and radiation therapy are the same for cervical malignancies in their early stages. This study additionally showed that patients treated with extensive surgery had a more favourable outcome than those treated with radiation therapy for ADC histology (Popovic, Bojic, Bojic, Vukmirovic, & Juskovic, 2024; Zhu, Chen, Sun, & Zhu, 2024).

Despite this, ADC has a less favourable outcome than the squamous subtype, even though previous research has not revealed any variations in prognosis among these two histologies. Thus, the described case addresses significant concerns in healthcare since early diagnosis enables efficient treatment, which lowers morbidity and mortality despite the relatively small body of research and instances. While it is evident that the interaction between the methods of morphological criteria analysis, immunohistochemistry, and staging was crucial for the management of the case and is essential to confirm the diagnosis, the significance of working together to identify the pathology deserves to be emphasized (Aggarwal, Jain, Garg, & Parihar, 2024; Akers, Read, Feldman, Gooden, & English, 2024; El Emrani, Nooij, Lap, & van der Meeren, 2024).

It is noteworthy to emphasize that, while they are uncommon and have a low prevalence, ovarian metastases resulting from primary cervical tumours, particularly those from squamous cell carcinoma (SCC) associated with adenocarcinoma (ADC), can happen, making diagnosis and appropriate treatment challenging. Since the other indicators are not as trustworthy, an immunohistochemistry examination using the p16 marker is required to demonstrate that the second lesion is a malignant carcinoma or metastasis of the adenocarcinoma ADC. Endocervical adenocarcinoma ADC can be used to show if ovarian metastases are present if the test is positive. To determine the International Federation of Gynaecology and Obstetrics (FIGO) staging and the best course of treatment, it is crucial to forecast and assess the disease's prognosis using clinicopathological variables and imaging studies (X. Chen et al., 2024; Liu, Zhang, & Yang, 2024).

Ethical Committee Permission

The study was approved by Hayatabad Medical Complex and informed consent was taken from the patient.

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