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Synchronous primary endometrial adenocarcinoma and primary squamous cell carcinoma of the cervix: A case report and literature review

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ABSTRACT

The synchronous occurrence of primary endometrioid endometrial adenocarcinoma and primary squamous cell carcinoma of the cervix is exceedingly rare. Ovarian and endometrial cancers represent the most frequently observed forms of synchronous gynaecological malignancies. In contrast, in less than 1 % of cases, endometrial cancer coexists with primary cervical cancer. Considering the unique characteristics of each primary malignancy, the management of synchronous tumours of the female genital tract poses significant challenges and requires a multidisciplinary, tailored approach to treatment.

This report concerns the case of a 63-year-old woman who underwent radical hysterectomy, bilateral salpingo-oophorectomy and bilateral pelvic lymph node dissection following a histological diagnosis of a poorly differentiated squamous cell carcinoma on cervical biopsy. Histological assessment of the surgical specimen also confirmed a primary grade I endometrioid endometrial adenocarcinoma confined to the endometrium and grade 3 squamous cell cancer of the cervix. The patient was successfully treated with adjuvant vaginal brachytherapy after primary surgery.

Synchronous endometrial adenocarcinoma and squamous cell carcinoma of the cervix is rare and associated with a poor prognosis. Fewer than ten cases could be found in the medical literature. This report raises awareness and adds to the study of an unusual synchronous cancer of the female genital tract and contributes evidence to advance the development of standardized treatment protocols.

1. Introduction

Synchronous gynaecological malignancies are rarely encountered; however, when they arise, these unique clinical entities can present diagnostic and therapeutic challenges. The incidence of synchronous primary invasive tumours of the female genital tract is approximately 1–6% [1]. The most common synchronous gynaecological neoplasms (SGNs) are endometrial and ovarian cancers [2]. While this combination is rare, it is even less common to encounter concomitant primary endometrial cancer and primary cervical cancer.

Given that the multiple primary tumours involved in synchronous gynaecological malignancies originate from distinct sources, the mutational profiles of each tumour differ significantly. Stewart et al. highlighted the importance of distinguishing between synchronous malignancy and metastatic disease [3]. This demarcation facilitates appropriate staging, prognostication and management [3]. Tumours with the most diagnostic difficulty are primary endometrial and primary *endo*-cervical adenocarcinomas [3]. Therefore, an integrative approach to treatment that considers the differences in the pathological features and genetic constitutions of each tumour is necessary [4]. For this reason, in 2020, the WHO updated its 2014 classification of cervical squamous cell carcinomas (SCC) to categorize SCC into HPV-associated and HPV-independent types [5]. Similarly, new classifications for cervical adenocarcinomas were made that provide a framework for understanding the pathogenesis and histopathological characteristics of these tumours and contribute to a clearer diagnosis where difficulty exists [5].

Due to the paucity of publications on synchronous endometrial adenocarcinoma and SCC of the cervix, there are no standardized treatment protocols. However, a multimodal approach to treatment that

Abbreviations: CT, Computed tomography; WHO, World Health Organization; SGN, Synchronous gynaecological neoplasms; SCC, Squamous cell carcinoma; LLETZ, Large loop excision of transformation zone; MRI, Magnetic resonance imaging; NCCN, National Comprehensive Cancer Network.

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includes surgical staging and adjuvant radiotherapy with considerations for chemotherapy appears to improve patient outcomes [6].

This case report highlights a rare finding of primary grade I endometrioid endometrial adenocarcinoma diagnosed after the patient underwent a radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node dissection for poorly differentiated squamous cell carcinoma identified on LLETZ. Histopathology demonstrated the coexistence of a primary grade I endometrioid endometrial adenocarcinoma. This appears to be the first reported case of a synchronous primary squamous cell cervical carcinoma and primary endometrial adenocarcinoma in the Caribbean.

2. Case Presentation

A 63-year-old woman was referred to the gynaecologic oncology clinic with poorly differentiated squamous cell carcinoma of the cervix. Several weeks earlier she had had an abnormal Pap smear, which could not rule out high-grade squamous intraepithelial lesion (HSIL), followed by a large loop excision of the transformation zone (LLETZ) and endocervical curetting. Histopathological assessment of the sample taken during the LLETZ procedure highlighted CIN III with positive deep and lateral margins (Fig. 1). The endocervical curetting demonstrated invasive, poorly differentiated squamous cell carcinoma with a positive immunohistochemical stain for AE1/AE3. Unfortunately, immunohistochemical staining for p16 was not available in that facility. The invasive tumour measured 3.9 mm across in maximum dimension and was consistent with at least stage IA2 disease.

The patient denied any history of postmenopausal bleeding or postcoital bleeding and had an uncomplicated menstrual history. She experienced deep dyspareunia and vague pelvic pain, which prompted her initial assessment. The patient had type II diabetes, treated with metformin 500 mg twice daily, had a history of a benign thyroid nodule and had undergone a total thyroidectomy approximately 13 years previously. Her gynaecological history was otherwise unremarkable. She had five children and no personal or family history of cancer. She had no previous Pap smears for comparison, denied any history of smoking and had not used any form of contraception or exogenous estrogens in the last 15 years.

The patient's body mass index (BMI) was 32.3 kg/m^2 on clinical assessment. At the same time, an abdominal examination demonstrated a mobile 10-week-sized uterus and a vaginal examination highlighted a 2 cm long mobile cervix with no evidence of parametrial invasion. Blood investigations, including a complete blood count and renal and liver function tests, were within normal parameters.

A computed tomography (CT) scan of the chest, abdomen and pelvis was requested for completion staging. The uterus was normal in size, and the endometrial cavity appeared uniform, with an endometrial thickness of 0.2 cm. There was no pelvic, retroperitoneal or inguinal lymphadenopathy noted on the abdominopelvic CT. There was also no evidence of regional or distant metastatic disease. Considering these CT findings, radiological features were consistent with cervical cancer, at least stage IA2, according to the revised FIGO 2018 staging for cervical cancer or T1a2N0M0 according to the TNM staging.

The optimal mode of management was discussed at the multidisciplinary team (MDT) meeting, and the patient underwent a radical hysterectomy, bilateral salpingo-oophorectomy and bilateral pelvic lymph node dissection. Histopathological assessment of the surgical specimen demonstrated a stage 1A2 primary grade 1 endometrioid carcinoma (according to FIGO 2023 staging for endometrial cancer) or T1aN0M0 with less than 50% myometrial invasion, no lymphovascular invasion and clear, negative margins (Fig. 2). The cervix showed a high-grade squamous intraepithelial lesion (HSIL/CIN III) with no residual squamous cell carcinoma identified.

The patient's postoperative course was uneventful. The case was discussed at the MDT meeting, and the patient was deemed a suitable candidate for vaginal brachytherapy based on the National Comprehensive Cancer Network (NCCN) framework for endometrial carcinoma.

The patient continued treatment at the medical oncology clinic and was also undergoing follow-up at the gynaecological oncology clinic with interval clinical assessments and interval imaging studies and had had no recurrence at the time of writing.

3. Discussion

Multiple primary malignancies (MPM) can originate from single or multiple anatomical organs [7]. According to the North American Association of Central Cancer Registries, MPM may be subdivided into synchronous and metachronous malignancies [8]. Synchronous MPM involves two primary cancers occurring simultaneously or within a maximum timeframe of six months, while metachronous MPM involves two primary cancers that occur in sequence or more than six months apart [7]. Synchronous gynaecological malignancies are rare, with an estimated incidence of 0.7% - 1.8% [9]. The most common synchronous primary tumours of the genital tract are ovarian and endometrial cancers (40% - 53%) [10]. Epidemiological studies describe numerous risk factors for developing synchronous gynaecological tumours, and these include age and menopausal status, human papillomavirus (HPV) infection, obesity, exposure to unopposed estrogen, genetic

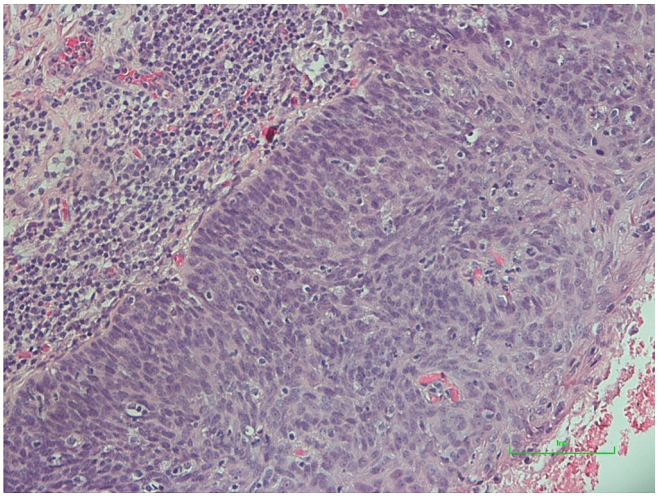

Fig. 1. Histopathology of the LLETZ specimen demonstrates CIN III with squamous differentiation.

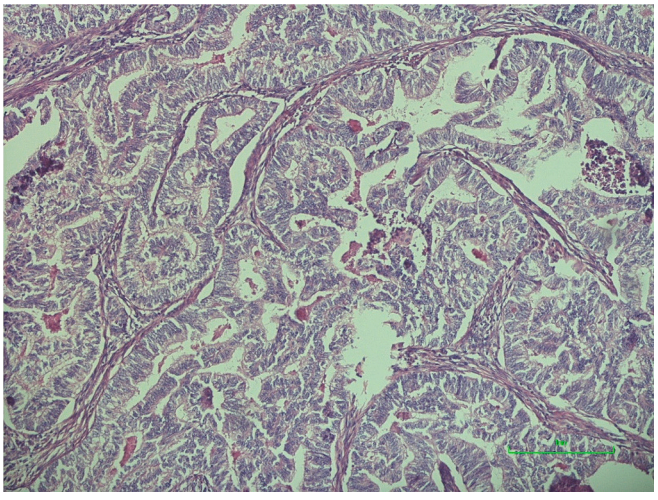

Fig. 2. Histopathology of the surgical specimen demonstrates endometrioid endometrial adenocarcinoma.

predisposition, such as Lynch syndrome, immunosuppression and smoking [11].

Based on histopathological and molecular patterns, the most common histological subtypes of synchronous endometrial and cervical cancer include endometrioid endometrial adenocarcinoma and squamous cell carcinoma (SCC) of the cervix [1]. The pathogenesis of synchronous endometrial adenocarcinoma and SCC of the cervix remains unelucidated; however, certain studies suggest that exposure of tissues of the female genital tract to certain carcinogens during embryological development predisposes to an intrinsic susceptibility that may influence the risk of developing a second primary tumour [11].

Moreover, genetic defects in mismatch repair genes may be responsible for a small subset of synchronous tumours observed similarly in colon, rectal and gastric cancers [11]. Lastly, mutations of the p53 gene, crucial for regulating cell cycle progression, apoptosis and genomic stability, may be indicated in synchronous tumours involving primary endometrial adenocarcinoma and primary SCC of the cervix [3]. In endometrial adenocarcinoma, particularly in serous and high-grade subtypes, p53 gene mutations are prevalent and are associated with poor prognostic outcomes [3]. Similarly, in SCC of the cervix, disruptive p53 mutations contribute to the evasion of apoptosis and enhanced tumour survival [3].

Synchronous endometrial adenocarcinoma and SCC of the cervix produce early signs and symptoms that prompt patients to seek medical care, unlike ovarian malignancies. Patients may present with abnormal uterine bleeding, intermenstrual bleeding, postcoital bleeding, and urinary or gastrointestinal symptoms [1]. In rare instances, patients may present deep dyspareunia and vague pelvic pain, as in the case presented. At present, the diagnosis of synchronous malignancies depends on histopathological assessment [6]. While most cases of synchronous cancers are diagnosed from the analysis of resected surgical specimens, the diagnostic accuracy can be improved with fractional curettage and cervical cytology testing when contact bleeding is observed on assessment [1]. According to Gates et al., to diagnose synchronous tumours, the following criteria should be fulfilled – (a) each tumour should present a definite picture of malignancy, (b) each tumour should be histologically distinct, and (c) the possibility of metastasis must be excluded [12]. In the case presented, each of these criteria was fulfilled.

However, further cytogenetic analyses such as immunohistochemistry, molecular tests such as microsatellite instability, and screening for mutations in female genital tract tumour genes like PTEN, TP53, KRAS and CTNNB1 are often required [6]. The distinction between a primary cervical and a primary endometrial malignancy is important for optimal patient management. The most common immunohistochemical markers are p16 and hormone receptors (estrogen and progesterone receptor (ER/PR)) [13]. High-risk HPV-related cervical carcinomas exhibit diffuse moderate to strong expression of p16, while endometrial endometrioid adenocarcinomas of all grades display variable patchy p16 expression [13]. In contrast, high-risk HPV-related carcinomas are typically negative for ER/PR expression, while endometrial endometrioid adenocarcinoma express ER and PR, either alone or in combination [13]. Both AE1 and AE3 are cytokeratins that are utilized to confirm and characterize the epithelial origin of the tumour cells and differentiate the tumour from non-epithelial subtypes such as sarcomas or lymphomas – tumours that do not express epithelial cytokeratins [1]. Due to the limited availability of molecular testing and screening tests for genetic mutations in the patient's clinical setting, only immunohistochemistry staining with AE1/AE3 was utilized. In this case, p16 and ER/PR testing were not done.

Currently, there are no standardized treatment protocols for synchronous endometrial adenocarcinoma and SCC of the cervix; however, a multimodal approach to treatment appears to improve patient outcomes. In most cases, the final clinical diagnosis of synchronous gynaecological tumours occurs after surgical intervention; therefore, treatment modalities depend independently on the established strategy for each tumour [6]. Both tumours are treated simultaneously considering several parameters such as the patient's age, histological type, clinical stage, grade and presence of lymphovascular invasion [6]. Depending on the stage of cervical cancer, treatment may include total abdominal hysterectomy with or without sentinel lymph node biopsy and pelvic lymph node dissection or radical hysterectomy with pelvic lymph node dissection with consideration for adjuvant chemoradiotherapy or, in advanced stages, chemoradiation [14]. In contrast, for stage IA, well-differentiated endometrial adenocarcinoma, a total hysterectomy, and bilateral salpingo-oophorectomy with lymph node assessment for staging (sentinel node or pelvic lymph node dissection) are performed. The patient described in the present report underwent a radical hysterectomy, bilateral salpingo-oophorectomy and bilateral pelvic lymph node dissection. Sentinel lymph node assessment was unavailable at the institution the patient attended.

Adjuvant chemoradiotherapy is typically considered based on the postoperative FIGO staging [15]. In advance-stage synchronous tumours, adjuvant chemotherapy that includes a combination of taxane and carboplatin or taxane and cisplatin is generally recommended [6]. According to the NCCN framework for endometrial carcinoma, locoregional radiotherapy, particularly vaginal brachytherapy, demonstrates efficacy for early-stage uterine cancer and reduces the risk of local recurrence in the following circumstances: patients over 60 years old, the presence of lymphovascular invasion and high-risk histological subtypes [14,15]. In the present case, the patient underwent vaginal brachytherapy, based on the histological subtype of the synchronous tumours, to render her disease-free and reduce the risk of recurrence [16].

The prognostic outcomes for patients diagnosed with synchronous primary endometrial and cervical cancers are closely associated with the clinical stage at the time of diagnosis [17]. Generally, synchronous tumours exhibit a worse prognosis than their metachronous counterparts; however, they demonstrate a higher survival rate than those observed in metastatic cases [17]. Due to the paucity of cases, evaluating prognostic factors is also challenging. Patients should be followed up with interval HPV testing of the vaginal vault, regular pelvic and rectal examinations and surveillance for metastatic disease or suspected recurrence.

In conclusion, synchronous primary endometrioid endometrial adenocarcinoma and primary squamous cell carcinoma of the cervix represent a notably rare clinical entity, with an incidence falling within the lower percentile range of all gynaecological malignancies. Clinically, these patients may present with overlapping symptoms that require thorough assessment, advanced imaging techniques and histopathological evaluation to confirm the dual primary nature of such tumours. The treatment of synchronous gynaecological tumours is particularly challenging and necessitates a tailored approach combining surgical intervention, radiotherapy and possibly chemotherapy, depending on the stage and characteristics of each tumour. Given the complexity of managing synchronous gynaecological cancers, the role of a multidisciplinary team is paramount. Ultimately, given the rarity of synchronous primary endometrial adenocarcinoma and SCC of the cervix, the study of this unique entity not only provides insights into the biological behaviour of these tumours but contributes to the evidence to the development of standardized treatment protocols in the future.

Contributors

Vishal Bahall contributed to patient care, conception of the case report and rafting and supervision of the manuscript.

Lance De Barry contributed to patient care, drafting the manuscript, undertaking the literature review and revising the article critically important intellectual content.

Ryan Charles contributed to patient care, drafting the manuscript and revising the article critically for important intellectual content.

Stefan Baldeo contributed to patient care, drafting the manuscript and revising the article critically for important intellectual content.

All authors revised the draft and approved the final manuscript.

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Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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