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Diagnostic Pitfalls and Immunohistochemical Hallmarks of a Rare FIGO Stage IIIC1 Cervical Mesonephric Adenocarcinoma: A Case Report

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1. Abstract

1.1. Background

Cervical mesonephric adenocarcinoma (MA) is an extremely rare non-HPV-associated cervical carcinoma (NHPVCC). Its characteristic endophytic growth frequently leads to false-negative routine screenings and misleading radiological presentations, severely complicating early diagnosis.

1.2. Case Presentation

We present a rare case of FIGO 2018 Stage IIIC1 cervical MA in a multiparous woman characterized by a one-year diagnostic delay. Initially presenting with lower abdominal distension, the endophytic mass was sonographically misdiagnosed as a benign leiomyoma. Despite the subsequent onset of contact bleeding, routine exfoliative cytology and HPV testing remained negative. The diagnostic challenge was further compounded when an initial outside-hospital biopsy suffered from severe cell crush artifacts, completely obscuring the morphological architecture. Definitive diagnosis was ultimately achieved at our tertiary centre via an ultrasound-guided core needle biopsy. The well-preserved tumour tissue exhibited classic tubular and microcystic patterns. A targeted immunohistochemical (IHC) panel confirmed diffuse positivity for CD10 and TTF-1, alongside a non-HPV-associated "patchy" p16 expression. Following an open radical hysterectomy and systematic lymphadenectomy, final pathology confirmed deep stromal invasion and bilateral pelvic lymph node metastasis. Adjuvant concurrent chemoradiotherapy (CCRT) was strongly recommended.

1.3. Conclusion

Clinicians must maintain a high index of suspicion for endophytic cervical masses mimicking leiomyomas, especially when routine screenings are negative. Accurate diagnosis relies heavily on mitigating crush artifacts during biopsy and utilizing a precise IHC panel (CD10, TTF-1, patchy p16) to differentiate MA from common mimics.

2. Introduction

Mesonephric adenocarcinoma (MA) of the cervix is an extremely rare non-HPV-associated cervical carcinoma (NHPVCC) originating from Wolffian duct remnants [1,2]. Due to its rarity and characteristic endophytic growth pattern, early-stage MA is frequently clinically occult. This often leads to false-negative results in routine screenings (Pap/HPV tests) and misleading imaging findings that mimic benign lesions like cervical leiomyomas, resulting in significant diagnostic delays.

Histopathological diagnosis is the gold standard but remains highly challenging. Small biopsy specimens are exceptionally susceptible to severe crush artifacts, which distort the typical tubular or microcystic structures. Consequently, a specific immunohistochemical (IHC) panel is crucial. The co-expression of CD10 and TTF-1, alongside a "patchy" p16 staining pattern, serves as the definitive diagnostic hallmark to differentiate MA from other cervical adenocarcinomas [3-5].

Here, we present a challenging case of FIGO 2018 Stage IIIC1 cervical MA with bilateral pelvic lymph node metastasis following a one-year diagnostic delay. Initially misdiagnosed as a leiomyoma and confounded by severe crush artifacts during the first biopsy, the diagnosis was ultimately established via precise IHC profiling. By highlighting these clinical and pathological pitfalls, we aim to improve diagnostic awareness and discuss the management of this rare, locally advanced NHPVCC variant.

3. Case Presentation

3.1. Medical History

A multiparous woman (gravida 4, para 2) presented with a one-year history of persistent lower abdominal distension. She had no history of abnormal cervical screening prior to the onset of her current symptoms, and her past medical and surgical histories were otherwise unremarkable.

3.2. Presentation and Work-Up

In May 2025, an initial pelvic ultrasound revealed a 23 × 22 mm hypoechoic cervical mass, which was clinically misdiagnosed as a benign leiomyoma, prompting conservative observation. Despite the subsequent development of prolonged menstruation and contact bleeding, a routine cervical cancer screening (exfoliative cytology and HPV testing) in October 2025 yielded a false-negative result. By February 2026, the mass had rapidly enlarged to 44 × 39 × 30 mm with prominent internal vascularity. The patient underwent a laparoscopic cervical mass excision at a local hospital; however, severe crush artifacts distorted the cellular architecture of the biopsied tissue, precluding a definitive diagnosis.

Upon referral to our tertiary centre, a contrast-enhanced pelvic MRI demonstrated a 4.8 cm endophytic cervical lesion highly suspicious for malignancy (Figure 1).

3.4. Surgical Treatment

In April 2026, the patient underwent an open radical hysterectomy (Type C), bilateral salpingo-oophorectomy, and systematic pelvic and para-aortic lymphadenectomy. Due to an intraoperative finding of a concurrent left ureteral calculus with hydronephrosis, a multidisciplinary approach was utilized to successfully place a left ureteral double-J stent.

3.5. Pathological Findings

To circumvent the prior crush artifacts, an ultrasound-guided core needle biopsy was performed prior to the radical surgery, revealing classic tubular and microcystic architectural patterns (Figure 2). A targeted immunohistochemical (IHC) panel was definitive: tumour cells were diffusely positive for CD10, TTF-1, and Pax-8. Crucially, p16 exhibited a non-HPV-associated "patchy" staining pattern, and estrogen/progesterone receptors were negative (Figure 3).

The final surgical pathology confirmed a 4.8 cm cervical mesonephric adenocarcinoma (MA) with deep stromal invasion. Lymph node dissection revealed bilateral pelvic lymph node metastasis, while para-aortic nodes were negative. The disease was definitively staged as FIGO 2018 Stage IIIC1 (pT3N1M0).

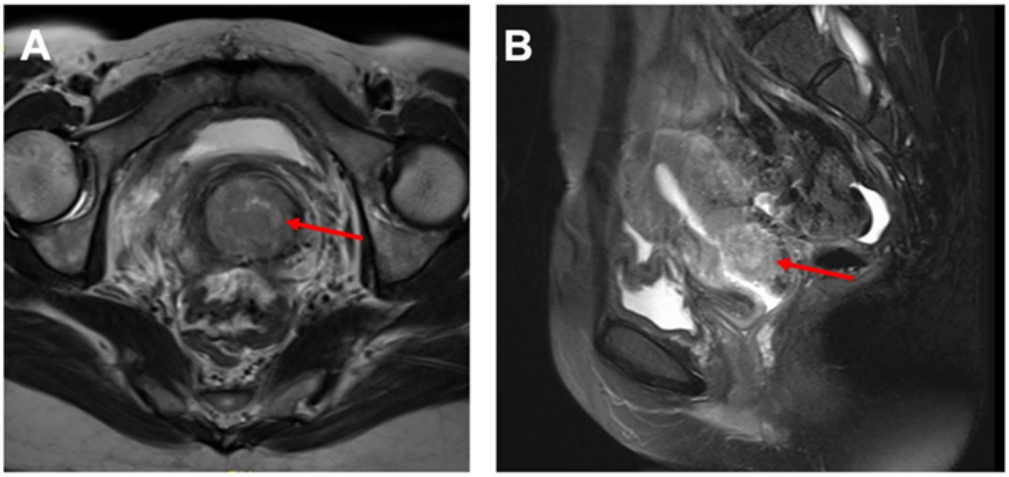

Figure 1: Preoperative pelvic magnetic resonance imaging (MRI) of the cervical mesonephric adenocarcinoma. (A) Axial and (B) sagittal views reveal a large (4.8 cm), heterogeneous, endophytic mass (indicated by red arrows) deeply infiltrating the cervical fibromuscular stroma. The tumour expands the cervix while maintaining a relatively intact external contour, a deceptive radiological feature that strongly mimics a benign cervical leiomyoma and significantly contributed to the initial diagnostic delay.

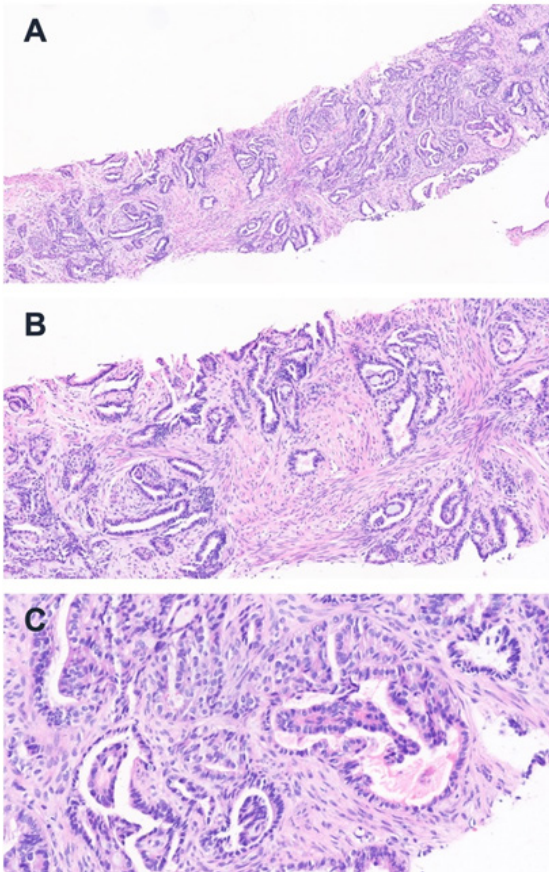

Figure 2: Histopathological evaluation of the ultrasound-guided core needle biopsy of the cervical mass. The well-preserved tissue, devoid of prior crush artifacts, allows for definitive morphological assessment (Hematoxylin and eosin [H&E] stain). (A) Low-power view (original magnification, ×5) reveals an infiltrative proliferation of neoplastic glandular structures within the dense cervical fibromuscular stroma. (B) Intermediate-power view (original magnification, ×10) highlights the classic tubular and microcystic architectural patterns characteristic of mesonephric adenocarcinoma. (C) High-power view (original magnification, ×20) demonstrates well-defined neoplastic tubules lined by a single layer of cuboidal to low columnar epithelial cells, containing characteristic focal eosinophilic intraluminal secretions.

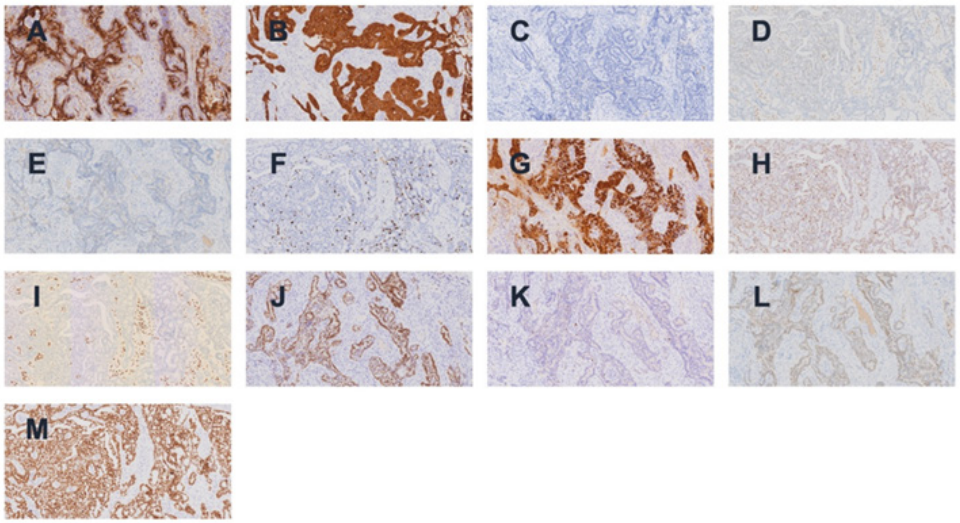

Figure 3: Comprehensive immunohistochemical (IHC) profiling establishing the definitive diagnosis of cervical mesonephric adenocarcinoma. The tumour cells display a highly specific IHC signature confirming mesonephric differentiation while rigorously excluding other cervical or endometrial malignancies (All images: original magnification, ×20). (A) CD10 exhibits characteristic strong luminal (apical) and partial cytoplasmic positivity, and (B) CK7 demonstrates diffuse and strong cytoplasmic expression. (C) CK5/6 is completely negative, effectively excluding squamous differentiation. (D) Estrogen receptor (ER) is negative, arguing against a metastatic endometrioid origin, alongside negative staining for (E) GATA3. (F) Ki-67 nuclear staining highlights the active proliferative index of the neoplastic cells. Crucially, (G) p16 displays a characteristic "patchy" staining pattern, definitively ruling out an HPV-associated etiology. (H) p53 shows a variable, wild-type nuclear expression, while (I) p63 is negative, further excluding squamous components. Markers supporting a Müllerian/mesonephric origin include weak to moderate nuclear positivity for (J) PAX2 and diffuse nuclear positivity for (K) PAX8. (L) Progesterone receptor (PR) is also negative. Finally, (M) TTF-1 shows diffuse and strong nuclear positivity, representing a highly specific diagnostic hallmark for mesonephric adenocarcinoma.

3.6. Adjuvant Therapy

The patient had an uneventful postoperative recovery and was discharged with the ureteral stent in situ. Given the aggressive biological behaviour of this rare NHPVCC variant and multiple high-risk pathological features (large tumour size, deep stromal invasion, and lymph node positivity), adjuvant concurrent chemoradiotherapy (CCRT) was strongly recommended by the multidisciplinary tumour board.

4. Discussion

4.1. The Deceptive Nature of NHPVCC and Ultrasound Differential Diagnosis Traps

The most profound clinical lesson of this case lies in the prolonged one-year diagnostic delay. Despite presenting with persistent lower abdominal distension and subsequent contact bleeding, the patient's routine cervical cancer screening (both exfoliative cytology and HPV DNA testing) consistently yielded false-negative results. This dual clinical deception stems directly from the distinct anatomical and biological characteristics of cervical mesonephric adenocarcinoma (MA) as a non-HPV-associated cervical carcinoma (NHPVCC).

Arising from the remnants of the mesonephric ducts located deep within the lateral cervical stroma, MA typically exhibits a pronounced endophytic growth pattern 6. In its early stages, the ectocervix may appear entirely normal, concealing the lesion within the endocervical canal or deep fibromuscular stroma. Consequently, on transvaginal ultrasound (TVUS), early-stage MA is easily misidentified as a common benign cervical leiomyoma.

However, the chronological evolution of this patient's imaging findings offers a critical point for clinical reflection. A typical leiomyoma presents as a well-circumscribed, hypoechoic mass, with colour Doppler flow imaging (CDFI) demonstrating peripheral circular vascularization. In contrast, as this patient's tumour progressed, its sonographic features transformed to display ill-defined margins and rich internal vascular signals. This intense internal vascularity reflects active tumour neovascularization and serves as a critical malignant "red flag" that distinguishes a benign myoma from an infiltrative endophytic malignancy. Furthermore, the rapid volumetric doubling within a short interval (enlarging from 23 mm to 44 mm) is incompatible with the natural history of a typical leiomyoma.

This scenario emphasizes that clinicians must maintain a high index of suspicion; for patients presenting with an endophytic cervical mass characterized by ill-defined margins, rich internal blood flow, and rapid growth, a malignant process cannot be ruled out by a negative routine screening. Advanced imaging such as pelvic MRI and deep tissue biopsy must be implemented promptly.

4.2. Overcoming Cell Crush Artifacts and the Precise Immunohistochemical Chain

While histopathological evaluation remains the gold standard for diagnosing MA, this case highlights a major pathological trap encountered during the initial work-up. The specimen from the first laparoscopic excision at the outside hospital suffered from severe crush artifacts. In small or fragmented biopsies, particularly within the dense and fibrous cervical stroma, tumour cells are highly susceptible to mechanical compression. This results in artificially elongated, hyperchromatic nuclei and obscured cell boundaries, which completely mask the characteristic tubular or microcystic architectural patterns of MA. Such artifacts frequently lead to a misdiagnosis of a high-grade undifferentiated carcinoma or sarcoma. At our institution, an ultrasound-guided core needle biopsy successfully circumvented these artifacts, providing well-preserved tissue that allowed clear morphological visualization.

When morphological structures are obscured or atypical, establishing a precise immunohistochemical (IHC) evidence chain is indispensable for a definitive diagnosis. Cervical MA possesses a highly specific IHC profile, which can be categorized into lineage-specific and exclusionary markers:

Lineage-Specific Markers: The co-expression of CD10 (typically exhibiting apical/luminal or diffuse cytoplasmic positivity) and TTF-1 is highly definitive. Although TTF-1 is classically associated with pulmonary and thyroid carcinomas, its nuclear expression in mesonephric remnants and MA represents a unique "diagnostic signature" that strongly confirms a mesonephric origin, as demonstrated by the diffuse positivity in our patient [7,8].

Exclusionary Markers: The tumour cells exhibited a 'patchy' p16 staining pattern, which stands in sharp contrast to the diffuse, block-type positivity characteristic of HPV-associated cervical adenocarcinomas, thereby confirming its NHPVCC etiology [9,10]. Concurrently, the absence of estrogen receptor (ER) and progesterone receptor (PR) expression completely excluded a metastatic endometrioid adenocarcinoma, which represents one of the most common diagnostic mimics.

4.3. Surgical Dilemma and Multidisciplinary Management of Locally Advanced (FIGO Stage IIIC1) Disease

The majority of MA cases reported in the literature are diagnosed at an early stage (FIGO Stage I). In our case, owing to the initial diagnostic delay, the tumour had progressed to 4.8 cm with deep stromal invasion and bilateral pelvic lymph node metastasis, establishing a final classification of FIGO 2018 Stage IIIC1 (pT3N1M0). This represents a relatively rare presentation of locally advanced disease within the currently published MA literature.

For locally advanced cervical adenocarcinomas with a primary tumour size >4 cm (Stage IB3/IIIC1), the optimal choice between primary radical surgery and primary concurrent chemoradiotherapy (CCRT) remains a subject of ongoing debate [11,12]. In this patient, because an incomplete local excision had been performed prior to referral-which altered the regional anatomy and posed a potential risk of tumour cell spillage-our team opted for an open radical hysterectomy (Type C) combined with systematic pelvic and para-aortic lymphadenectomy. This aggressive surgical approach achieved maximal cytoreduction and

allowed accurate pathological staging.

Furthermore, the management of a complex pelvic comorbidity-concomitant left upper ureteral calculi with severe hydronephrosis-highlighted the value of a multidisciplinary team (MDT) approach. The successful intraoperative placement of a double-J stent not only preserved renal function but also ensured a safe anatomical environment for subsequent pelvic radiation, providing valuable management experience for complex gynecological malignancies.

4.4. Challenges and Exploration of Postoperative Adjuvant Therapy

Due to the extreme scarcity of cervical MA, current NCCN guidelines lack specific therapeutic recommendations for this histotype, and postoperative adjuvant management is typically extrapolated from conventional cervical adenocarcinomas13. This patient presented with a constellation of high-risk and intermediate-risk prognostic factors, including a primary tumour diameter >4 cm, deep stromal invasion (>1/2 fibromuscular wall), and pathologically confirmed bilateral pelvic lymph node metastasis.

According to the classic Gynaecologic Oncology Group (GOG) scoring systems (Sedlis criteria) and the Peters criteria, this patient met the absolute indications for adjuvant concurrent chemoradiotherapy (CCRT). The standard regimen involves pelvic external beam radiotherapy (EBRT) combined with weekly cisplatin or a cisplatin/paclitaxel doublet. Emerging data suggest that MA may possess a more aggressive biological behaviour and a higher propensity for early recurrence compared to conventional adenocarcinomas. Therefore, timely initiation of robust adjuvant CCRT and a rigorous, long-term follow-up strategy are critical to optimizing the long-term survival of patients with Stage IIIC1 disease.

5. Conclusion

Cervical mesonephric adenocarcinoma is an exceptionally rare and deceptive variant of non-HPV-associated cervical cancer. Clinically, when managing an endophytic cervical mass that mimics a benign leiomyoma on ultrasound and presents with false-negative routine screening results, a high index of clinical suspicion is mandatory. Pathologically, meticulous biopsy techniques must be employed to avoid diagnostic confusion caused by cell crush artifacts. Definitive diagnosis relies on a precise IHC panel consisting of CD10(+), TTF-1(+), patchy p16, and negative ER/PR expression. For locally advanced (Stage IIIC1) cases, a comprehensive approach comprising radical surgery, multidisciplinary management of pelvic comorbidities, and timely postoperative concurrent chemoradiotherapy represents the optimal clinical pathway to improve patient prognosis.

6. Acknowledgments

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7. Ethics Approval and Consent To Participate

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. The study protocol and the publication of this case report were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Guilin Medical University.

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