

The Diagnostic Conundrum of Recurrent High-Grade Vaginal Intraepithelial Neoplasia (VAIN) Following Definitive Cervical Cancer Treatment: A Case Report

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Abstract

Background: Cervical cancer management can be complex, particularly in cases with aggressive histopathology and atypical recurrence patterns. This report details the course of a patient with high-grade cervical carcinoma. **Case Presentation:** A 43-year-old female was initially diagnosed with a high-grade squamous intraepithelial lesion (HSIL) on biopsy. Following laparoscopic hysterectomy, final pathology revealed upstaging to FIGO stage pT1b2, Grade 3 squamous cell carcinoma (SCC). The patient received adjuvant concurrent chemoradiotherapy (CCRT) with Cisplatin. Initial surveillance was clear, but she later presented with neurological symptoms and an abnormal Pap smear, leading to a diagnosis of high-grade vaginal intraepithelial neoplasia (VAIN). Subsequent imaging confirmed disease recurrence with peritoneal metastasis. **Conclusion:** This case underscores the aggressive biological behavior possible in certain cervical carcinomas, even after standard definitive treatment. It highlights the diagnostic challenges of recurrence, including transiently benign biopsies, and emphasizes the need for vigilant, multimodal surveillance in high-risk patients.

Keywords

Cervical Cancer, Neoplasm Recurrence, Vaginal Intraepithelial Neoplasia, Chemoradiation, Case Report

1. Introduction

Cervical carcinoma, while largely preventable, continues to present significant clinical challenges, particularly in cases of high-risk histopathological features and atyp-

ical recurrence. The standard management for locally advanced disease, including radical surgery followed by adjuvant concurrent chemoradiotherapy (CCRT), is supported by trials demonstrating improved survival. However, a subset of patients experiences rapid, aggressive recurrence despite optimal initial therapy [1]. This case is unique in demonstrating a swift progression from early-stage diagnosis to metastatic disease, highlighting a potential gap in risk stratification for seemingly compliant patients and warranting further investigation into more robust predictive biomarkers [2].

The diagnostic odyssey in this case adds a layer of complexity to the literature on recurrent disease. Following initial treatment, the patient developed neurological symptoms and had cytological evidence of malignancy, yet subsequent biopsies yielded conflicting results, from high-grade vaginal intraepithelial neoplasia (VAIN) to benign inflammation. This inconsistency underscores a known challenge in gynecologic oncology: the limited sensitivity of biopsies for detecting microinvasive or multifocal disease [3]. This case exemplifies how such diagnostic uncertainty can lead to critical delays in confirming recurrence and initiating salvage therapy [4].

This case is unique in demonstrating a swift progression from early-stage diagnosis to metastatic disease, highlighting a potential gap in our current risk stratification models, which rely heavily on FIGO staging and histologic grade. This warrants further investigation into more robust predictive biomarkers, such as specific molecular profiles (e.g., PI3K/AKT/mTOR pathway mutations, TPS or CPS scores for PD-L1 expression), tumor microenvironment characteristics (e.g., CD8+ tumor-infiltrating lymphocyte density), or liquid biopsy markers (e.g., circulating tumor DNA/HPV DNA) to better identify patients with seemingly early-stage disease who harbor a high risk for aggressive, occult metastatic recurrence [2].

2. Case Presentation

Patient Information: The patient is a 43-year-old female, gravida 4 para 3 + 1, with no significant family history of gynecologic malignancies. Psychosocial history was non-contributory. The patient reported no routine cervical cancer screening (Pap smear or HPV test) in the five years preceding her presentation. Her initial and primary concern was abnormal uterine bleeding, characterized by menorrhagia and intermenstrual bleeding (**Table 1**).

Table 1. Comprehensive timeline of the patient’s diagnosis, treatment, and disease progression. Key events include initial presentation with bleeding, upstaging after hysterectomy, adjuvant chemoradiation, the development of a confounding VAIN diagnosis, and the eventual confirmation of metastatic recurrence leading to the initiation of palliative systemic chemotherapy.

Date	Event	Outcome/Finding
Mar-Apr 2023	Initial Presentation	Presented with menorrhagia and intermenstrual bleeding.
13-Apr-2023	Diagnostic hysteroscopy with curettage & cervical biopsy	Noted “abnormal anterior lip of the cervix.”

Continued

25-Apr-2023	Pathology results	High-Grade Squamous Intraepithelial Lesion (HSIL) ; invasion not assessed.
04-Jun-2023	Laparoscopic Hysterectomy & Bilateral Salpingectomy	Intraoperative bleeding (500 cc). Final pathology upstaged diagnosis.
19-Jul-2023	Final Surgical Pathology	Squamous Cell Carcinoma, Grade 3, pT1b2 (~4 cm, deep stromal invasion, close radial margin).
Aug 2023	Adjuvant Therapy	Completed Concurrent Chemoradiotherapy (CCRT) with weekly Cisplatin (40 mg/m ²).
22-Nov-2023	Surveillance PET scan	Significant improvement; no new FDG-avid lesions.
Dec-2023	Oncology follow-up	Diagnosed with bilateral ovarian vein thrombosis; started on Rivaroxaban.
Feb 2024	Signs of Recurrence	Presented with left-sided numbness. Pap smear showed “Malignant Cells Present.” Neurological workup (MRI, EEG) was largely inconclusive.
Dec-2024- May-2025	Examination under Anesthesia (EUA) with biopsies (x ₂)	Conflicting pathology: High-Grade VAIN (Dec) followed by benign squamous epithelium (May), creating diagnostic uncertainty.
Jun 2025	Advanced Diagnostic Imaging	
18-Jun-2025	PET FDG Whole Body	New FDG-avid right intrapelvic nodule and focal bowel uptake, concerning for recurrence/metastasis.
30-Jun-2025	CT Abdomen & Pelvis	Confirmed 0.9 cm soft tissue lesion in right hemipelvis, correlating with PET finding.
Nov 2025	Progression & New Intervention	
19-Nov-2025	Oncology consultation	Imaging confirmed recurrence with peritoneal metastasis . Tumor PDL-1 positive. Referral for salvage SBRT was rejected as the disease was now radiologically confirmed to be multifocal and metastatic (peritoneal involvement), placing it beyond the curative scope of any localized radiotherapy approach. The clinical decision was to prioritize systemic chemotherapy to address the widespread disease burden.
19-Nov-2025	Systemic Chemotherapy Initiated	Cycle 1: Carboplatin (AUC 5) + Paclitaxel (175 mg/m²) + Bevacizumab (15 mg/kg) . Plan for reassessment after 3 cycles.

Abbreviations: HSIL, High-Grade Squamous Intraepithelial Lesion; SCC, Squamous Cell Carcinoma; CCRT, Concurrent Chemoradiotherapy; VAIN, Vaginal Intraepithelial Neoplasia; EUA, Examination under Anesthesia; PET, Positron Emission Tomography; CT, Computed Tomography; SBRT, Stereotactic Body Radiation Therapy.

The diagnostic process utilized various methods. The initial diagnosis was established through cervical biopsy and pathology from a hysterectomy. Ongoing monitoring included Pap smears and advanced imaging, such as PET and CT scans, which were crucial for detecting recurrence, especially when biopsy results were ambiguous (indicating either VAIN or benign conditions) (**Figure 1**). This illustrates a significant diagnostic difficulty: the poor sensitivity of targeted biopsies for detecting micrometastatic disease, which led to a delay in confirming the recurrence, which was later identified on imaging. The diagnosis progressed from HSIL to SCC, and ultimately to recurrent SCC with peritoneal metastasis. Key prognostic factors included high-grade histology (Grade 3), deep stromal invasion, and PDL-1 expression.

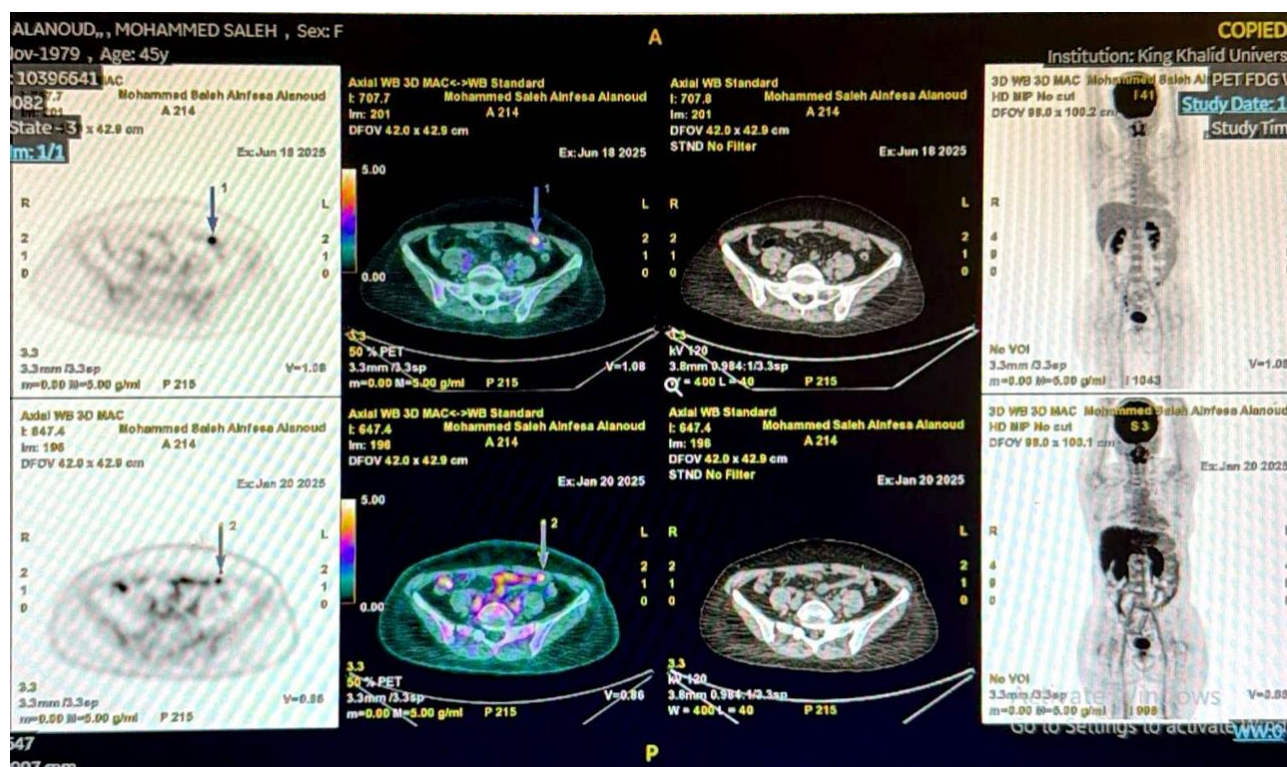


Figure 1. 18F-FDG PET/CT scan demonstrating disease recurrence. The panel displays axial PET (left), fused PET/CT (center), and non-contrast CT (right) images. The blue arrows (labeled 1 and 2) identify new, focal areas of intense radiotracer uptake (hypermetabolism) located in the right intrapelvic region and adjacent to bowel loops. These findings correspond to the rounded soft tissue lesion later characterized on CT, consistent with the diagnosis of recurrent squamous cell carcinoma with peritoneal metastasis.

The approach to therapeutic interventions evolved considerably as the disease progressed. Initially, a laparoscopic hysterectomy was performed as the primary surgical treatment. Following this, standard concurrent chemoradiotherapy (CCRT) was administered, which included weekly Cisplatin over a span of five weeks. Later, an exploration of salvage treatment options, specifically brachytherapy, was undertaken, followed by Stereotactic Body Radiation Therapy (SBRT). However, these options were ultimately not pursued. Due to confirmed metastatic progression, first-line systemic chemotherapy was initiated. The chosen regimen of Carboplatin, Paclitaxel, and Bevacizumab is a recognized first-line option for recurrent/metastatic disease. The finding that the tumor was PDL-1 positive carries significant implications for both prognosis and future treatment sequencing. While the current prognosis remains guarded given the aggressive, metastatic nature of the recurrence, PDL-1 positivity identifies a subset of patients who are more likely to respond to immunotherapy. This biomarker now provides a clear rationale for the potential future incorporation of immune checkpoint inhibitors (e.g., Pembrolizumab) into her treatment plan, should her disease progress on the current chemotherapy regimen.

Follow-up care consisted of continuous monitoring through serial imaging, routine clinic visits, and discussions in tumor board meetings. The outcomes of the treatments were mixed; while the initial interventions resulted in a clear PET

scan, the disease exhibited aggressive characteristics, leading to a subsequent metastatic recurrence. Although the patient managed to tolerate the initial CCRT, she experienced a significant complication—bilateral ovarian vein thrombosis—that necessitated long-term anticoagulation therapy. Attendance at scheduled appointments and adherence to the treatment plan were monitored through clinical visits. As for the response and tolerability to the new chemotherapy regimen, a reassessment is planned after the completion of three cycles.

3. Discussion

A key strength in managing this case was the adherence to standard oncologic protocols, including prompt surgical intervention followed by evidence-based adjuvant chemoradiation. The use of advanced, multimodal imaging (PET and CT) was crucial in resolving diagnostic uncertainty created by conflicting biopsy results and ultimately confirming metastatic recurrence. However, a significant limitation was the diagnostic challenge posed by the post-treatment field. The conflicting biopsy results, showing high-grade VAIN followed by benign epithelium, are unlikely to be due solely to sampling error. This discrepancy more profoundly reflects the known biological behavior of recurrent disease in this context: it is often patchy, multifocal, and can be obscured by post-radiation changes including inflammation and fibrosis. This creates a heterogeneous landscape where targeted biopsies can easily miss foci of malignancy, leading to false reassurance and critical delays in diagnosis, as exemplified here. This case underscores the limited sensitivity of biopsies in such a complex setting and argues for a lower threshold to employ advanced imaging to resolve uncertainty.

The study by Liao *et al.* (2011) [5] analyzed outcomes for 10 patients who developed vaginal intraepithelial neoplasia (VAIN) following radiation therapy (RT) for gynecologic cancer, comparing them to 23 non-irradiated VAIN patients. Their key finding was that the post-RT group had a significantly higher recurrence rate (OR 3.625) and a markedly elevated risk of progression to invasive cancer—3 of 10 patients (30%) in the RT group developed invasive carcinoma, compared to only 1 of 23 (4.3%) in the control group. This quantifies post-radiation VAIN as a highly aggressive, treatment-resistant condition.

Our case report provides a singular but powerful validation of these findings. Our patient, like those in Liao's cohort, developed high-grade VAIN after cervical cancer treatment involving CCRT. Her clinical course perfectly illustrates the "recalcitrant" nature described by Liao: despite diagnostic procedures, her disease proved difficult to eradicate and rapidly evolved into confirmed metastatic recurrence. This mirrors the high progression risk (30%) observed in the study, underscoring that VAIN post-radiation is not a benign finding but a serious harbinger of invasive disease that demands vigilant, aggressive management.

The case report by Elst *et al.* [6] presents a different scenario involving a patient who had an isolated vaginal recurrence of cervical cancer 18 years after initial treatment. This patient achieved a lasting complete pathological response of over

67 months following six cycles of combination chemotherapy, which included gemcitabine, vinorelbine, and cisplatin, and did so without the need for salvage surgery. In contrast, our case shows a notably more aggressive and rapid recurrence; our patient experienced a recurrence within just two years, with imaging revealing peritoneal metastasis, which classified her in the incurable and palliative-intent category. As a result, her treatment path was markedly different. Instead of aiming for potentially curative chemotherapy, she began first-line palliative chemotherapy consisting of carboplatin, paclitaxel, and bevacizumab. The main distinction between the two cases lies in the recurrence's pattern and timing: Elst's patient had a late, localized recurrence that was suitable for aggressive chemotherapy, whereas our patient faced an early, widespread metastasis that necessitated systemic palliative care.

The conclusions are rationalized by the disease's objective progression despite maximal initial therapy. The rapid upstaging post-hysterectomy, the development of VAIN, and the eventual radiographic confirmation of peritoneal metastasis all align with the known aggressive behavior of poorly differentiated, deeply invasive cervical carcinomas. The shift to systemic chemotherapy was necessitated by the confirmation of metastatic disease, which places it beyond the scope of curative local treatments like radiation. The chosen carboplatin-paclitaxel-bevacizumab regimen is a recognized first-line option for recurrent/metastatic disease, providing a rational therapeutic pathway.

4. Conclusion

The key lesson from this case is the aggressive nature of high-grade cervical carcinomas, which can progress to metastatic disease despite standard treatment. It highlights the necessity of vigilance for recurrence even with initially reassuring biopsies and advocates for advanced imaging in clinical decision-making. Additionally, it demonstrates the need for a flexible, multidisciplinary management approach, ready to shift from local therapy to systemic options as the clinical situation evolves. In this case, the multidisciplinary tumor board was instrumental in reconciling the conflicting biopsy and imaging findings, leading to the definitive imaging that confirmed metastasis and the subsequent collective decision to pivot from salvage radiotherapy to systemic chemotherapy.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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