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Late Deltoid Cutaneous and Axillary Recurrence of Cervical Squamous Cell Carcinoma: A Case Report Exploring the Locus Minoris Resistentiae Hypothesis

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Abstract

Cervical cancer typically spreads locally and through the pelvic and para-aortic lymphatic pathways; however, cutaneous metastases and axillary lymph node involvement are rare. This report presents a case involving this uncommon pattern of metastatic spread and discusses its clinical implications. A 67-year-old woman with a history of stage IIIB cervical squamous cell carcinoma, treated with concurrent chemoradiotherapy, had remained in complete remission for five years. Four years after receiving a COVID-19 mRNA vaccination in the left deltoid region, she developed a cutaneous metastasis strictly localized to the injection site, accompanied by ipsilateral axillary lymphadenopathy. Histopathological and immunohistochemical analyses confirmed metastatic squamous cell carcinoma positive for P40, P63, and pan-cytokeratin. A PET-CT scan demonstrated isolated hypermetabolic lesions in the left arm and axillary region. Systemic chemotherapy consisting of paclitaxel, carboplatin, and bevacizumab was initiated. This case illustrates the phenomenon of *locus minoris resistentiae*, in which injection-site tissue trauma and local inflammation may act as catalysts for metastatic localization. Clinicians should exercise increased vigilance when evaluating abnormalities at injection sites in patients with a history of malignancy.

Categories: Obstetrics/Gynecology, Oncology, Dermatology
Keywords: axillary metastasis, cervical cancer, covid-19 vaccine, cutaneous metastasis, locus minoris resistentiae, squamous cell carcinoma

Introduction

Cervical cancer is a major public health issue, with nearly 604,000 new cases diagnosed each year worldwide. It ranks fourth among the most common cancers in women and represents the fourth leading cause of cancer-related mortality in women, with a standardized mortality rate of 5.5 per 100,000 women [1]. This disease burden is particularly heavy in developing countries, especially in sub-Saharan Africa, where limited access to human papillomavirus (HPV) screening and preventive vaccination is the main determinant of persistent high incidence and mortality rates [2]. Despite therapeutic advances combining surgery, concurrent chemoradiotherapy, and brachytherapy, the overall five-year survival rate remains around 68.8%. This prognosis is closely dependent on the stage at diagnosis, ranging from 91.8% for localized disease to only 20.5% in distant metastatic settings [3].

The natural history of cervical carcinoma generally involves direct local extension to adjacent pelvic structures and predictable lymphatic dissemination to pelvic and para-aortic lymph nodes. When distant hematogenous metastases occur, they most frequently involve the lungs, liver, and bones [4]. Conversely, cutaneous metastases secondary to cervical cancer remain exceptional, documented in fewer than 2% of patients (ranging from 0.1% to 1.3%) and typically signaling widespread end-stage visceral dissemination [5]. Because axillary lymph nodes lie entirely outside the physiological lymphatic drainage pathways of the uterine cervix, isolated synchronous cutaneous and axillary involvement constitutes a highly atypical metastatic pattern.

Following mass immunization campaigns against COVID-19, various benign dermatological and immunological reactions have been documented at injection sites, including transient local reactogenicity, reactive axillary lymphadenopathy, and more unusual inflammatory manifestations. Cutaneous seeding at sites of prior mechanical trauma, iatrogenic punctures, or intramuscular injections has occasionally been described in oncological literature under the conceptual framework of the locus minoris resistentiae phenomenon, wherein localized tissue injury and microvascular alterations provide a transient microenvironment conducive to the arrest and extravasation of circulating dormant tumor cells [6,7]. However, whether localized vaccine-induced inflammation directly contributes to late metastatic entrapment or represents a purely coincidental spatial occurrence remains unproven.

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Herein, we report the case of a 67-year-old cervical cancer survivor who presented with late cutaneous metastatic recurrence localized in the left deltoid soft tissue at a previous COVID-19 mRNA vaccination site, accompanied by ipsilateral axillary lymphadenopathy. We frame this unusual presentation as an exploratory, hypothesis-generating observation to illustrate diagnostic pitfalls and highlight the necessity of maintaining vigilant clinical inspection and prompt biopsy for persistent, atypical nodules at prior puncture sites during long-term oncological surveillance.

Case Presentation

We report the case of a 67-year-old woman with insulin-dependent type 2 diabetes mellitus and hypertension, who presented with a newly developed cutaneous lesion. Her medical history was notable for stage IIIB squamous cell carcinoma of the cervix diagnosed in 2015, which had been definitively managed with concurrent chemoradiotherapy followed by brachytherapy. After an uneventful five-year surveillance period, she was declared in complete clinical and radiological remission in late 2020. In 2021, within the framework of the national immunization program, the patient received a standard primary two-dose regimen of a COVID-19 mRNA vaccine administered intramuscularly into the left deltoid muscle; no booster doses were subsequently recorded. Because immunization was carried out at an external community vaccination center, specific manufacturer data, proprietary brand names, batch numbers, and preservative profiles were not retrievable from the primary hospital records.

Approximately two years post-vaccination (four years following the completion of her initial five-year oncology surveillance), the patient noted the progressive appearance of a pruritic nodular lesion arising at the prior left deltoid injection site, a topographic correlation established through matching vaccination records and patient recall. This was accompanied by localized skin retraction and ipsilateral axillary lymphadenopathy. An initial dermatological assessment included a soft-tissue ultrasound, which revealed an infiltrative, retractile hypoechoic mass in the left upper arm associated with suspicious ipsilateral axillary lymph nodes. Subsequent bilateral mammography ruled out occult breast pathology, confirming isolated left axillary lymphadenopathy.

The patient was referred to the Department of Medical Oncology at Mohammed VI University Hospital in Marrakech. Physical examination revealed a firm, pruritic, irregular nodular plaque measuring 20 × 10 mm on the lateral aspect of the upper third of the left arm, exhibiting characteristic superficial cutaneous tethering (Figure *1*).



FIGURE 1: Clinical appearance of the cutaneous metastasis at the vaccination site

This figure shows an indurated, erythematous, and pruritic nodular lesion (measuring approximately 20 × 10 mm) with localized soft-tissue retraction on the lateral aspect of the upper left arm, strictly localized at the site of the previous COVID-19 mRNA vaccination.

In addition, two fixed, matted left axillary lymph nodes measuring 10 × 10 mm and 20 × 20 mm were palpated. A core needle biopsy was performed, specifically targeting the dominant, palpable retractile deltoid nodule.

Histopathological examination of the deltoid biopsy demonstrated infiltration of the deep reticular dermis and subcutaneous adipose tissue by nests of atypical squamous cells displaying nuclear pleomorphism and elevated mitotic activity. The overlying epidermis was entirely preserved, showing an intact baseline architecture without dysplasia, carcinoma in situ, or connection to the underlying dermal neoplasm. Immunohistochemical (IHC) analysis demonstrated diffuse, strong nuclear immunoreactivity for p40 and p63, alongside intense cytoplasmic positivity for pan-cytokeratin (AE1/AE3), consistent with poorly differentiated metastatic squamous cell carcinoma matching the archival profile of her primary cervical tumor (Figure *2*).

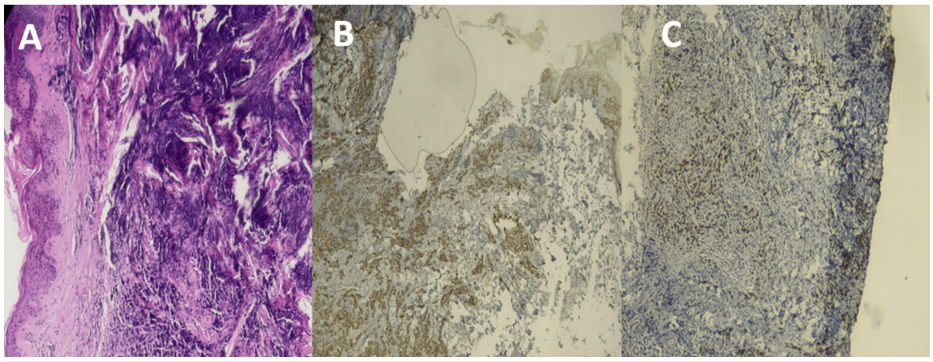


FIGURE 2: Histopathological and immunohistochemical findings of the cutaneous lesion

(A) Histopathological examination showing dermis infiltration by poorly differentiated carcinoma nests with nuclear pleomorphism and atypical mitoses (hematoxylin and eosin (H&E) stain, magnification ×200). (B) Immunohistochemical staining demonstrating strong and diffuse nuclear positivity for anti-P40 (magnification ×200). (C) Immunohistochemical staining showing diffuse nuclear positivity for anti-P63 (magnification ×200), confirming the diagnosis of metastatic squamous cell carcinoma.

Excisional biopsy of the left axillary lymph node confirmed metastatic moderately differentiated squamous cell carcinoma with lymphovascular space invasion, histologically concordant with both the cutaneous focus and prior cervical pathology (Figure *3*).

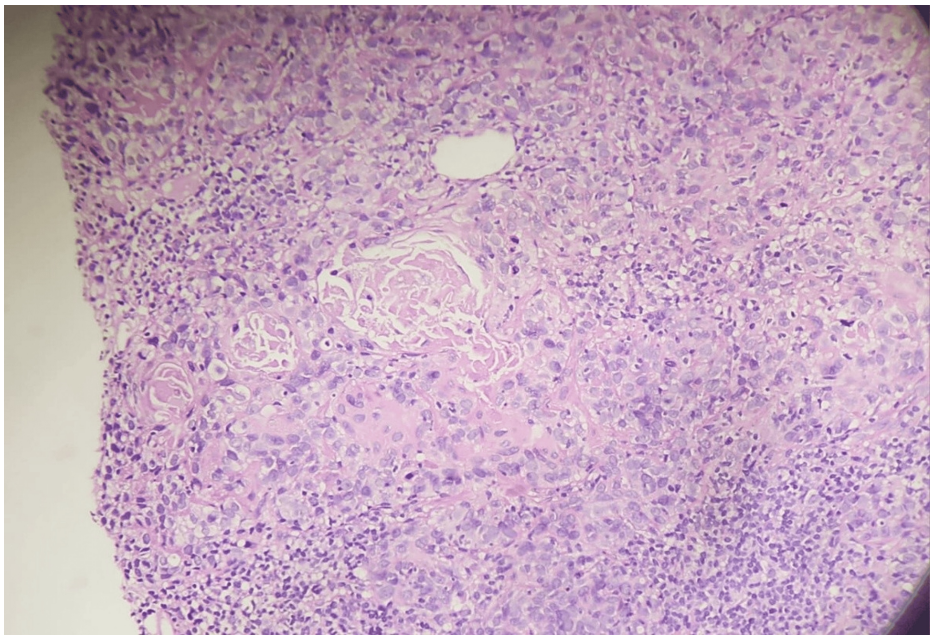


FIGURE 3: Histopathological examination of the left axillary lymph node biopsy

Axillary lymph node biopsy showing metastatic squamous cell carcinoma with keratin pearl formation (hematoxylin and eosin (H&E) stain, ×200).

Due to local public institutional resource constraints, retrospective molecular HPV genotyping, p16 IHC, and PD-L1 scoring could not be performed on the metastatic tissue.

A whole-body 18F-FDG PET-CT scan, obtained for comprehensive restaging, demonstrated intense tracer avidity within a contiguous cluster of five hypermetabolic subcutaneous nodules strictly localized within the left deltoid soft tissue around the clinical index lesion (measuring up to 22 × 33 mm, SUVmax 12.3) (Figure *4*).

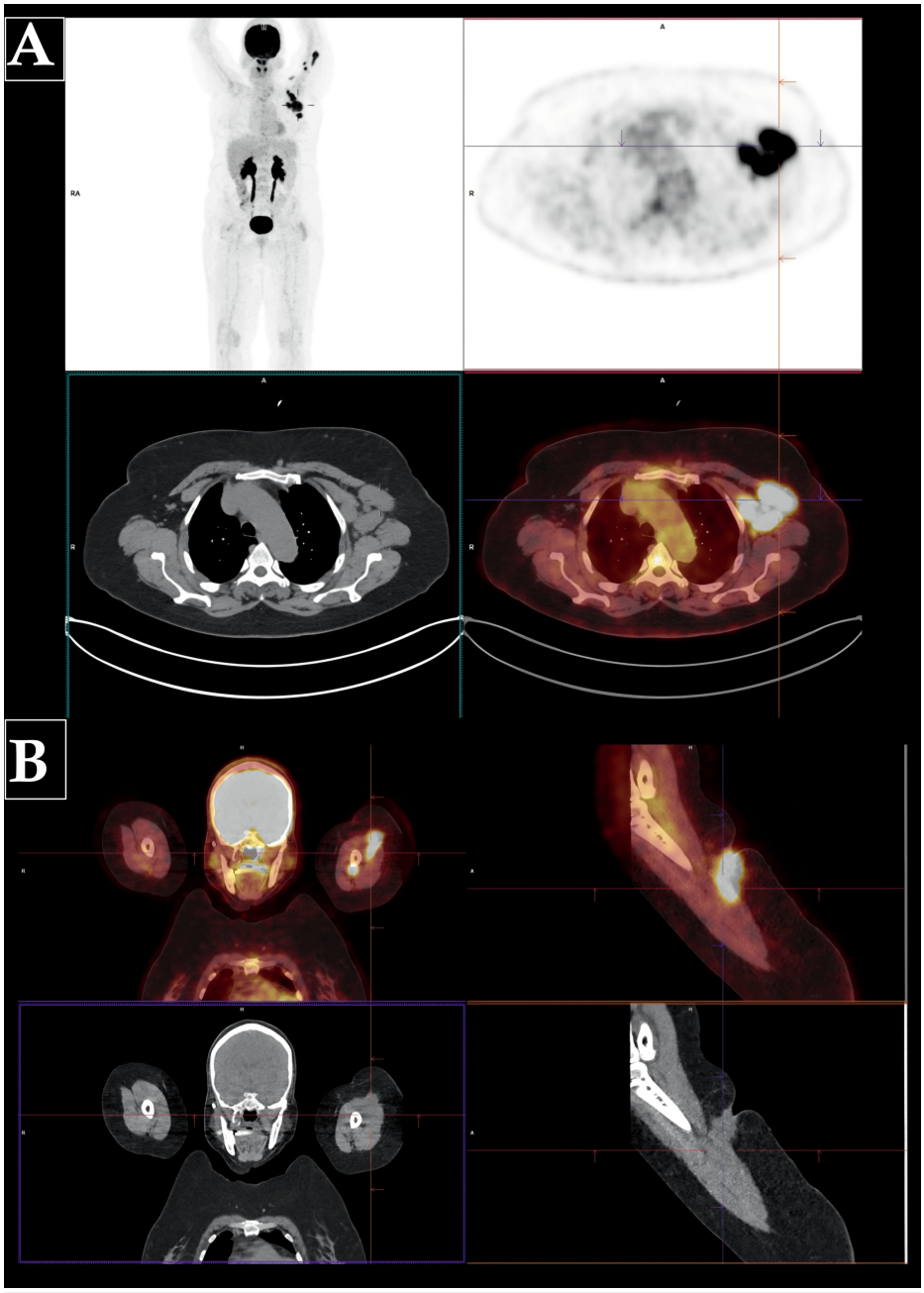


FIGURE 4: 18F-FDG PET-CT scan findings

(A) Whole-body maximum intensity projection (MIP) image displaying intense and exclusive pathologic 18F-FDG uptake confined to the left upper extremity and left axillary region, with no evidence of distant visceral, pelvic, or retroperitoneal recurrence. Axial views (PET, CT, and fused PET-CT) confirm a dominant, intensely hypermetabolic left axillary lymph node mass measuring up to 17 mm with an SUVmax of 16.0. (B) Coronal and sagittal coregistered CT and fused PET-CT sections of the left arm revealing an intensely FDG-avid subcutaneous nodular lesion on the lateral aspect of the upper third of the left arm (vaccine injection site), measuring up to 22 × 33 mm with an SUVmax of 12.3, accompanied by focal skin retraction and soft tissue infiltration.

18F-FDG PET-CT: fluorine-18 fluorodeoxyglucose positron emission tomography-computed tomography.

The scan also delineated prominent, hypermetabolic left axillary lymphadenopathy spanning Berg levels I through III, including a 16-mm level II node (SUVmax 16.0) and an adjacent 17-mm level III node (SUVmax 14.6). No evidence of locoregional pelvic recurrence, pulmonary or hepatic metastasis, or other distant metastatic foci was observed.

The clinical findings were reviewed at a multidisciplinary tumor board. Given this isolated atypical metastatic recurrence, systemic palliative therapy was initiated with a triweekly regimen combining paclitaxel (175 mg/m^2), carboplatin (AUC 5), and bevacizumab (15 mg/kg) every 21 days. Following six

completed cycles of chemotherapy, interval clinical evaluation and restaging imaging confirmed substantial regression of the left deltoid induration along with a partial metabolic response in the axillary lymph nodes, with acceptable hematological tolerance during continued maintenance surveillance.

Discussion

As a general rule, the emergence of cutaneous metastases stemming from cervical cancer is a rather unusual phenomenon [5,8]. They most often appear as a consequence of solid cancers such as those of the breast, head and neck, melanoma, or lung and usually indicate an advanced stage of the disease, associated with a poor prognosis; the overall long-term survival after the diagnosis of cutaneous metastasis, regardless of the primary cancer, is estimated to be 8.5 months [8,9].

Histologically, squamous cell carcinoma is the most commonly observed type in these cutaneous metastases [9,10]. This can be attributed to the fact that it is the most common histological type among primary cervical cancers and that the histology of the metastatic lesion often closely resembles that of the primary tumor [10,11].

These cutaneous metastases generally present as firm, non-ulcerated nodules, plaques, or inflammatory lesions with a telangiectatic appearance [10-12]. They most often occur on the abdominal wall, the anterior chest wall, the back, the upper and lower limbs, the vulva, or the scalp [11, 12]. Most of the time, they are asymptomatic or can cause itching, as is the case for our patient [9,11,12].

Cutaneous metastases of cervical cancer can manifest synchronously or, very rarely, after a long delay (beyond 10 years). They most often occur within the two years following initial treatment, with an average delay of 17 to 26 months [8,10]. This duration is directly correlated with the initial FIGO stage, significantly decreasing as the stage progresses (3 to 4 months for stage IV compared to 37.6 months for stage I) [10].

The lymphatic drainage of the cervix is directed toward three groups of pelvic lymph nodes: internal iliac, external iliac, and obturator. From these lymphatic relays, the tumor is likely to spread to the para-aortic lymph nodes and ascend along the thoracic duct, which drains into the venous circulation at the confluence between the left subclavian vein and the internal jugular vein [13,14].

The axillary lymph nodes only drain the upper limb and the thoracic wall, without a direct lymphatic connection to the pelvis [14]. Axillary involvement therefore implies prior hematogenous dissemination. We hypothesize an anatomical sequence involving initial hematogenous seeding within the deltoid soft tissue, followed by secondary locoregional lymphatic permeation toward the ipsilateral axillary basin. This model reconciles systemic vascular dissemination with the regional anatomical continuity observed clinically.

A paramount diagnostic imperative in such presentations is differentiating secondary metastatic recurrence from a primary cutaneous squamous cell carcinoma (cSCC) or a Marjolin-type malignant degeneration arising in a puncture cicatrix. Although primary cSCC and cervical SCC share standard squamous lineage markers, consistently demonstrating robust immunopositivity for p40, p63, and high-molecular-weight cytokeratins, several distinct clinicopathological features firmly support a secondary metastatic origin in our patient. Histopathologically, the atypical squamous nests infiltrated the deep reticular dermis and subcutaneous adipose tissue beneath a completely preserved, intact epidermis devoid of architectural dysplasia, full-thickness atypia, or connection to the underlying malignancy. Conventional primary cutaneous SCC characteristically originates from intraepidermal dysplasia or pre-existing actinic damage, features entirely absent here. Furthermore, Marjolin ulcer characteristically develops within chronically inflamed, non-healing scars, burn contractures, or persistent sinus tracts; our patient maintained unbroken, non-ulcerated skin without antecedent chronic scar tissue. While retrospective high-risk HPV molecular typing (p16 IHC or in situ hybridization) was not feasible due to local public hospital resource constraints, the matching morphological architecture with the patient's historical cervical tumor and the synchronous development of bulky, multi-level axillary nodal metastases strongly favor a metastatic attribution over a de novo cutaneous malignancy.

The strict topographic co-localization between the deltoid injection site and the subsequent subcutaneous lesion evokes the pathophysiological concept of locus minoris resistentiae [6,7]. Within oncological biology, mechanical trauma, needle puncture, or localized iatrogenic inflammation can transiently alter microvascular architecture, provoking focal endothelial hyperpermeability and local secretion of pro-inflammatory cytokines, chemokines, and growth factors (including IL-6, TNF-alpha, and VEGF) [7,15]. Such localized microenvironmental perturbations have been hypothesized to facilitate the entrapment, arrest, and extravasation of low-level circulating tumor cells, or to disrupt dormant microniches. Similar spatial clustering has occasionally been reported following surgical incisions, intramuscular injections, or radiotherapy portals. However, considering the prolonged temporal latency of several years between immunization and clinical recurrence, and the lack of histologically confirmed persistent local inflammation, a direct causative role for the mRNA platform or specific formulation excipients cannot be definitively affirmed. Consequently, this report must be interpreted strictly as an exploratory, hypothesis-generating clinical observation rather than proof of vaccine-induced reactivation.

Although a few isolated cases of cervical cancer metastases to the upper limbs or axillary soft tissues have been reported, metastatic dissemination confined to a previous vaccination injection site in cervical squamous cell carcinoma remains an exceptionally rare phenomenon.

This work has certain limitations inherent to the case report format. The temporal-spatial coincidence between the vaccine injection and the appearance of the metastasis, although suggestive, does not allow for the establishment of a formal causal link in the absence of direct molecular evidence of the proposed mechanism (clonal tracing of tumor cells, characterization of the local inflammatory microenvironment). The locus minoris resistentiae hypothesis therefore remains, at this stage, a plausible explanatory model rather than a causal demonstration. Furthermore, complete pharmacological data regarding the actual commercial brand, proprietary platform name, and batch or lot number of the injected COVID-19 vaccine could not be obtained from the patient's records, excluding any brand-specific reactogenicity. Additionally, no testing for HPV was performed on the metastatic sample due to institutional resource limitations, which could have provided definitive molecular proof of cervical provenance.

The clinical implications of this case are of major importance. Clinicians must exercise heightened vigilance when assessing persistent or progressive skin lesions or lymphadenopathy at injection sites in patients with a history of cancer. Although vaccination is strongly recommended for vulnerable oncology patients, the persistence of an atypical nodule or adenopathy after vaccination warrants prompt radiological evaluation followed by early biopsy in order to rule out metastatic recurrence at a locus minoris resistentiae and to ensure appropriate palliative or systemic management.

Conclusions

In conclusion, cutaneous and axillary metastases from cervical squamous cell carcinoma remain exceptionally rare. While localized mechanical or inflammatory microenvironment alterations suggest the locus minoris resistentiae phenomenon as an exploratory biological hypothesis, a direct causal relationship cannot be established from a single clinical observation. The principal clinical lesson is, therefore, any persistent, indurated, or atypical cutaneous and soft-tissue lesion emerging at a prior puncture or injection site in a cancer survivor warrants prompt histopathological evaluation to exclude late atypical recurrence and guide timely systemic therapy.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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