



Case report

Multiple recurrences from cervical cancer presenting as skin metastasis of different morphologies

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A B S T R A C T

Skin metastasis is an infrequent manifestation in oncology, with reported incidence of about 1.3% in cervical cancer. When present, it usually signals advanced disease with very limited, mostly palliative treatment options. Here we present a patient who was diagnosed with cervical cancer at an early stage and later recurred twice with skin lesions of different morphologies.

1. Introduction

The most common malignancies that are associated with cutaneous spread include breast, lung, colon, oral mucosa and melanoma (Schwartz, 1995). Incidence in cervical cancer has been reported to be around 1.3% (Imachi et al., 1993). Common morphologic presentations include nodules, plaques or inflammatory telangiectasias, although many others have been described (Imachi et al., 1993; Agrawal et al., 2010; Palaia et al., 2002; Burbano et al., 2018). Suspicious skin lesions found on physical examination at any point should be biopsied, as the time to presentation can range anywhere from weeks to years (Agrawal et al., 2010).

2. Case report

A 60 year-old female, gravida6, para5, abortion1 with well controlled diabetes and hypertension was diagnosed with FIGO Stage IIa cervical cancer following an abnormal pap smear in 2011. She was clinically asymptomatic. Physical exam was significant for a 2x2cm necrotic lesion in the cervix extending in a thin plaque to the right vaginal fornix. Pathology showed a tumor with glandular and squamous differentiation consistent with an adenosquamous carcinoma of the cervix (Fig-1A). CT scan did not show any evidence of metastatic disease. She underwent Radiation Therapy (45Gy in 25 Fractions with brachytherapy and 9Gy boost) to the pelvis but did not receive chemotherapy for unclear reasons.

After a disease-free interval of 38 months (2014), surveillance PAP-smear revealed high grade squamous intraepithelial lesion (HGSIL) with features suggestive of invasion. Vaginal, left pelvic wall, and

periurethral biopsies showed the squamous cell carcinoma component of the tumor (Fig. 1B). Whole-body CT scan was remarkable for high aorto-caval and pelvic adenopathy. Repeat radiation therapy was not thought to be feasible and patient received chemotherapy with 6 cycles of carboplatin and paclitaxel. Repeat imaging after chemotherapy revealed resolution of adenopathy and she was placed on clinical and radiological surveillance.

In April 2016 patient was diagnosed with asymptomatic local recurrence on a surveillance CT scan but refused to get further treatment. In November 2016, she presented with multiple pruritic pearly hyperpigmented dry papules on lower abdomen and thighs (Fig. 2A). A CT scan of her chest, abdomen and pelvis showed that the cervical mass was stable with no evidence of any other metastases. Biopsy from the left abdomen skin lesions showed a poorly differentiated tumor similar to previous cervical primary (Fig. 2B). She received chemotherapy, which was interrupted several times due to multiple urinary tract infections. The rash completely resolved and CT scan did not reveal any measurable cervical mass.

In March 2018, she presented with a new non-pruritic patchy erythematous skin rash over the anterior lower abdomen and back (Fig. 3A) and a large non-tender left breast mass with fixed nipple occupying the whole left breast. CT scan showed multiple new liver lesions consistent with metastases. A repeat left abdomen skin biopsy showed a similar tumor to prior biopsies (Fig. 3B). A left breast biopsy showed findings consistent with metastatic adenosquamous carcinoma from the cervix which was positive for the following stains: mucicarmine in lumina-like structures indicative of glandular differentiation, p16, CK7, CEA, high molecular weight cytokeratin 34βE12, patchy weak GATA3, focal p63, weak patchy PAX8, focal weak estrogen

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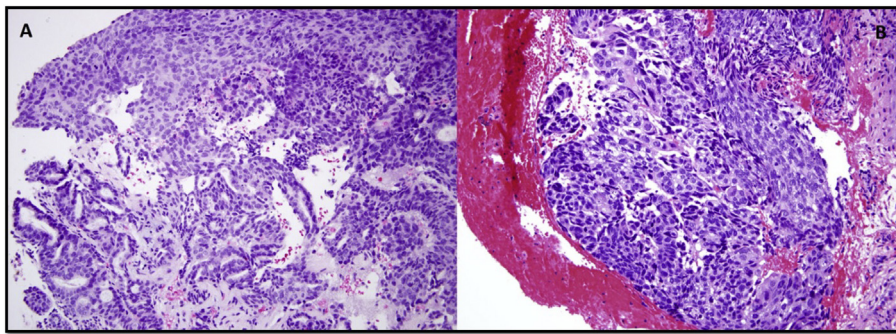


Fig. 1. A: Cervical biopsy from 2011 shows adenocarcinoma with squamous and glandular differentiation in the upper and lower fields of the photo respectively (Hematoxylin & Eosin stain, magnification x100). B: Periurethral biopsy from 2014 shows the squamous cell carcinoma component with focal keratinization seen as pink eosinophilic area at upper left (Hematoxylin & Eosin stain, magnification x200). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

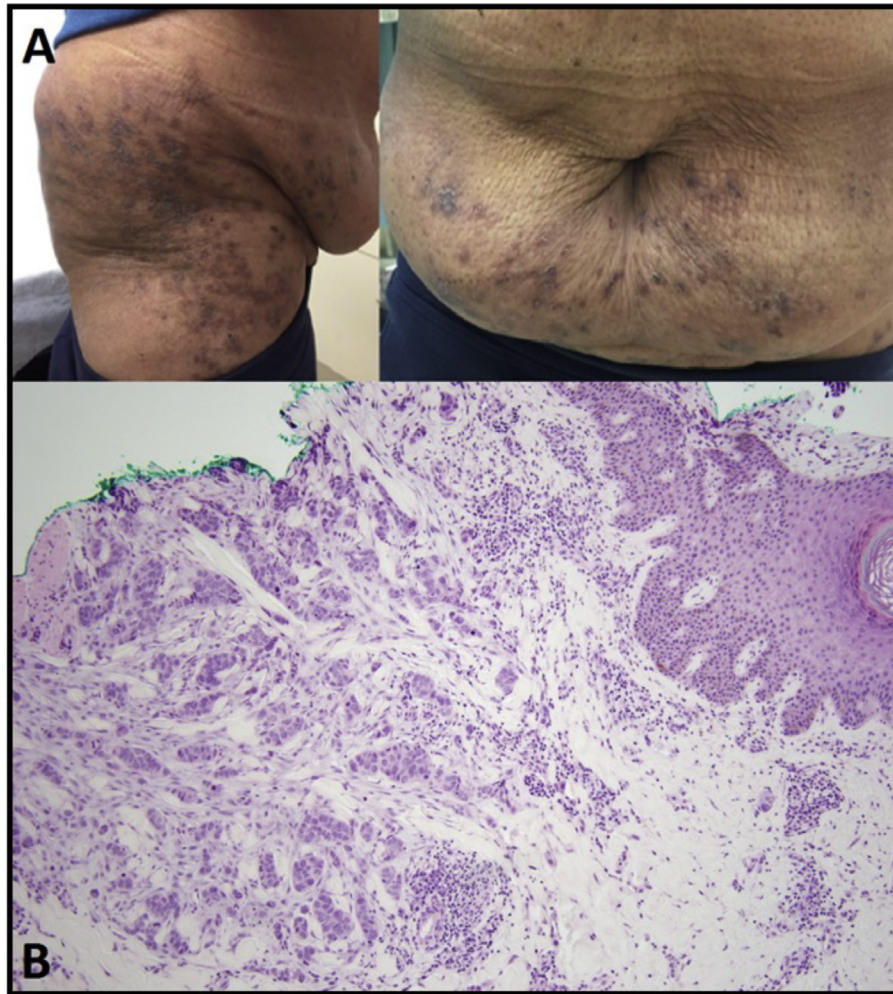


Fig. 2. First episode of skin metastasis in 2016.

A: Abdominal rash extending to thighs. Hyperpigmented and pearly papules, some grouped, no vesicles or pustules. B: Histology of abdomen skin biopsy showing the poorly differentiated carcinoma (Hematoxylin & Eosin stain, magnification x100).

receptor, and in situ hybridization was positive for high risk human papilloma virus. (Fig. 4). She was started on single agent liposomal doxorubicin but she passed away after 1 cycle of chemotherapy, 7 years from the original diagnosis and 4 years since disease recurrence.

3. Discussion

Skin metastases are a rare phenomenon most often associated with malignancies of the breast, lung, colon, oral mucosa and melanoma (Schwartz, 1995). On a retrospective analysis of 1190 patients, its overall incidence during the course of cervical cancer was reported to

be around 1.3% (Imachi et al., 1993). While initial studies reported a higher incidence with adenocarcinoma and undifferentiated carcinomas, squamous cell pattern is being increasingly recognized as the histology in such cases (Imachi et al., 1993; Agrawal et al., 2010). Metastatic route is still unclear, with some studies suggesting a retrograde spread of tumor secondary to lymphatic obstruction. A hematogenous pattern of dissemination has also been reported in the literature (Palaia et al., 2002; Pertzborn et al., 2000). Interestingly, many cases have been associated with development of lesions over sites of previous skin injuries, surgical incisions, drains and radiation therapy needles, raising the possibility of direct implantation of tumor cells (Pertzborn

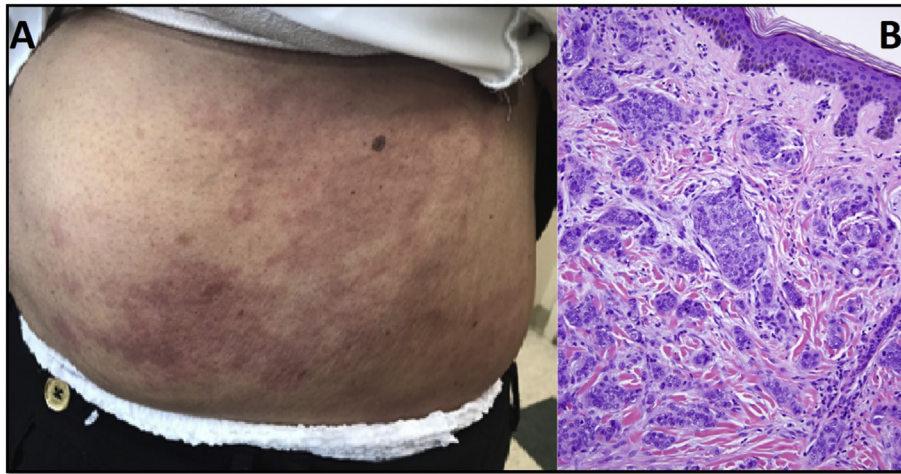


Fig. 3. Second episode of skin metastasis in 2018.

A: Erythematous, confluent patches over abdomen extending to lower back. B: Histology of skin biopsy showing tumor similar to first episode of skin metastasis (Hematoxylin & Eosin stain, magnification x200).

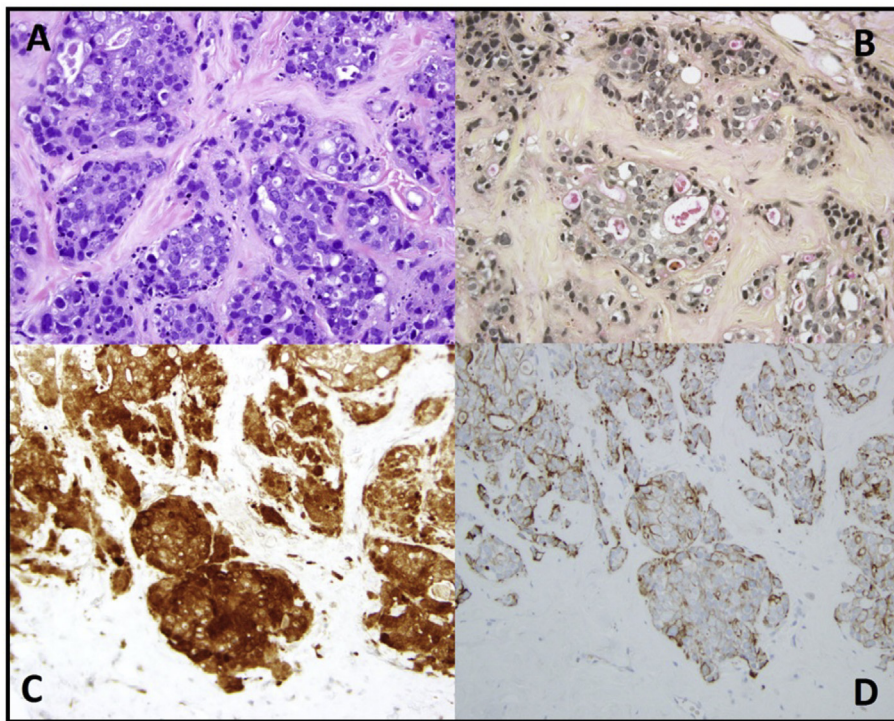


Fig. 4. Breast biopsy from 2018.

A: Histology of the adenosquamous carcinoma with areas of lumina-like structures (Hematoxylin & Eosin stain, magnification x400). B: Mucicarmine stain shows positive pink staining in the small lumina-like structures supportive of glandular differentiation (Magnification x400). C: P16 immunohistochemistry strongly stains the tumor cells (Magnification x400). D: High Molecular Weight Cytokeratin 34βE12 immunohistochemistry highlighting the tumor (Magnification x400).

et al., 2000; Yamashita et al., 2009; Basu and Mukherjee, 2013; Ozmen et al., 2009; Behtash et al., 2002; Srivastava et al., 2005).

Morphology of metastatic skin manifestations from cervical cancer can be diverse, including nodules, plaques and inflammatory telangiectatic lesions. Less common presentations are alopecia and lymphangitic carcinomatosis mimicking contact dermatitis (Imachi et al., 1993; Agrawal et al., 2010; Palaia et al., 2002; Burbano et al., 2018). Neoplastic cells usually involve the dermis but occasionally may infiltrate the epidermis as well (Alcaraz et al., 2012). Although distant lesions on scalp, upper chest wall and distal extremities have been reported, abdominal wall and lower extremities are common sites (Agrawal et al., 2010; Hayes and Berry III, 1992). It usually occurs in cases of tumor recurrence, but it has also been reported as part of primary disease (Pertzborn et al., 2000). The average time to presentation ranges from 16.9–20.7 months, although it can vary from several weeks to several years (Agrawal et al., 2010). Our patient first

presented with skin metastasis 70 months after her initial diagnosis.

This case was unique due to the fact that patient's skin rash was the main presentation for systemic recurrence. Furthermore, she relapsed twice with lesions of different morphologies, initially having dry, itchy and hyperpigmented plaques that resolved with chemotherapy and then an erythematous, patchy, non-pruritic rash a year later.

Cutaneous metastasis usually signals advanced, pre-terminal disease and treatment is largely palliative with no standard protocol. Even though chemotherapy with paclitaxel has been demonstrated to induce complete response (Palaia et al., 2002), very few patients survive beyond 6–12 months (Imachi et al., 1993; Pertzborn et al., 2000; Srivastava et al., 2005). Other treatment options include radiation, surgical excision and electro-chemotherapy, which involves concomitant local application of a cytotoxic agent and electric impulses to ensure better drug diffusion into cells (Agrawal et al., 2010; Benoulaid et al., 2016). It should be noted that, given the high rate of recurrences

reported on previous surgical incisions, judicious treatment planning with cautious handling of tissues may help prevent cutaneous spread of the disease. Extension of radiation therapy fields to cover surgical sites should also be considered (Basu and Mukherjee, 2013).

The time from diagnosis of the first skin lesion to death in our patient was 17 months, which is consistent with the reported poor prognosis. Other predictors of unfavorable prognosis in cervical cancer include advanced age, adenosquamous histology, anemia and positive pelvic lymph node metastasis (Hong et al., 2004). Despite cutaneous metastasis being a rare occurrence, a thorough skin exam should be performed on routine visits of all patients, with low threshold for skin biopsy.

Author contributions

Writing-original draft preparation T.A., V.K.; Writing-Review & Editing S.G.; Pathology images and description N.M., N.R.; Supervision N.R., S.G.

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