

Case report

Metastatic cervical adenocarcinoma to the breast: A case report and literature review

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ABSTRACT

Breast metastases from gynecologic cancers are rare. Cervical cancer most commonly metastasizes to the lung, liver or bone. When cervical cancer metastasizes to the breast, the presentation is usually a solitary breast mass; rarely, however, breast metastases can mimic inflammatory breast cancer. We present a case of metastatic cervical adenocarcinoma presenting clinically as inflammatory breast cancer and review the relevant literature.

1. Introduction

Though the rates of cervical cancer have decreased dramatically in developed countries over the past 50 years, it is still the second most common cancer in women in developing countries (Frumovitz, 2017). By contrast, it is the 13th most commonly diagnosed cancer in Canada and the United States (American Cancer Society, 2018). Cervical cancer metastasizes through direct invasion of local structures, hematogenous dissemination to the lungs, liver or bone, or dissemination through the lymphatic system (Aziz and Aziz, 2017). It is rare for any gynecological cancer to metastasize to the breast but when this occurs the typical presentation is of a solitary mass (Toombs and Kalisher, 1977).

We report the unusual case of a young woman with advanced cervical adenocarcinoma who developed left axillary adenopathy and the clinical appearance of inflammatory breast cancer (IBC) on the ipsilateral side.

2. Case presentation

A 35-year-old woman with a history of chlamydia and drug abuse presented with postcoital spotting, and shortly thereafter vulvar swelling, left groin rash, edematous left breast, diffuse musculoskeletal pain, vertigo and fatigue. The patient's human immunodeficiency virus serology was negative; however she was found to have Group B streptococcal bacteremia and infective endocarditis for which she was started on intravenous antibiotics. A computed tomography (CT) scan of the chest, abdomen and pelvis revealed a cervix mass, left-sided hydronephrosis and retroperitoneal lymphadenopathy. Physical examination

revealed a firm 6 cm mass replacing the cervix with left pelvic sidewall and right parametrial involvement and pap smear showed adenocarcinoma of endocervical origin. A transvaginal ultrasound also revealed a 1.9×0.7 cm echogenic area in the cervix. Given the clinical picture consistent with an advanced stage cervical cancer and the patient's critically ill status, the decision was made to continue to treatment without biopsy. The patient was diagnosed with FIGO stage IIIB adenocarcinoma of the cervix and was treated with curative intent involving external beam radiotherapy (EBRT), 45Gy in 25 fractions to the pelvis and para-aortic regions, followed by high-dose rate interstitial brachytherapy, 28Gy in four fractions. No concurrent chemotherapy was offered due to ongoing bacteremia and endocarditis.

The patient continued to experience erythema and fullness of the left breast throughout her treatment course. The original CT scan identified asymmetric skin thickening in the left breast and mildly prominent left axillary nodes (Fig. 1A). A bilateral mammogram was performed at that time and was reported to show benign breast disease (BIRADS-2; Fig. 1B). An ultrasound revealed subcutaneous edema and skin thickening suggestive of mastitis. The patient denied intravenous drug use but soft tissue infection in the area could not be excluded. As the patient was already on antibiotic therapy for her bacteremia and endocarditis, no changes were made to her management at this time.

Near the end of her treatment, the patient was admitted to hospital to facilitate her brachytherapy. At that time, further asymmetry of the breasts with central erythema and a peau d'orange appearance extending over the lateral two-thirds of the left breast was noted. There were no palpable masses in either breast; however, a mat of lymph nodes was identified in the left axilla, along with a 1.5 cm firm node in

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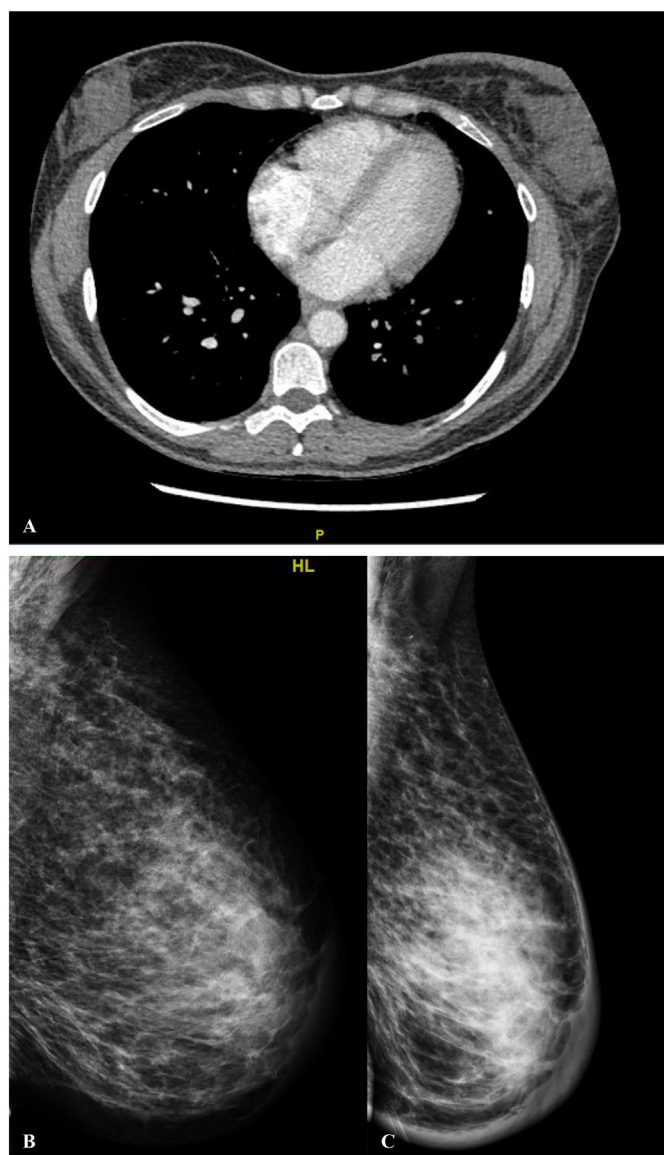


Fig. 1. A Representative axial CT slice showing asymmetrical skin thickening overlying the left breast. B Mammogram of the left breast performed at the time of initial breast inflammation demonstrating mild skin thickening and subcutaneous edema with no visible masses. C Repeat contrast-enhanced mammogram performed two months later showing an edematous left breast with diffuse skin thickening and accentuated trabecular markings.

the left mid-cervical chain. Mammography was repeated with contrast, identifying diffuse skin thickening over the left breast, dense nodes within the left axilla and linear calcifications in the upper outer quadrant of the left breast extending into the left axilla. The mammogram was reported as highly suspicious for inflammatory breast cancer (BIRADS-5; Fig. 1C) and biopsy of the axillary mass was performed. Pathology revealed high grade poorly differentiated adenocarcinoma with negative reactivity for estrogen, progesterone and human epidermal growth factor receptor 2 (HER2) receptors. With clinical correlation, the patient was diagnosed with triple negative, locally advanced inflammatory breast cancer.

Given the highly unusual presentation, the patient's case was reviewed at a multidisciplinary meeting including radiation, medical and surgical oncology, radiology and pathology. Thorough review of her prior imaging and biopsies was undertaken. Immunohistological studies of the axillary biopsy showed diffuse and intense reactivity for p16 and negative reactivity to mammoglobin (Fig. 2), suggesting a cervical

origin. Given this evidence, the patient was informed that she most likely had metastatic cervical adenocarcinoma, rather than a second breast cancer.

The patient's endocarditis resolved and she completed six cycles of chemotherapy consisting of carboplatin and paclitaxel with bevacizumab. Repeat CT showed resolution of the disease within the left axilla and she went on to receive consolidative radiotherapy to the left axilla, 40Gy in 15 fractions. Her disease is stable at 6 month follow-up.

3. Discussion

Metastatic disease of the breast is most commonly secondary to a contralateral breast malignancy, but has been reported in melanoma, lymphoma, sarcoma, and in carcinoma of the lung, ovary, gastrointestinal tract, genitourinary tract, thyroid, vagina, cervix and endometrium (Akçay, 2002). However, the incidence of any metastasis to the breast is rare, comprising only 0.5–1.5% of breast malignancies (Hajdu and Urban, 1972). There is some indication that breast metastases may be underdiagnosed, with an autopsy series placing the incidence closer to 6% (Di Bonito et al., 1991). Nevertheless, there have been only sporadic reports of cervical carcinoma metastasizing to the breast and even fewer presenting as IBC (Sabatier et al., 2012; Moore et al., 1998). Several other cancers, ovarian and gastric in particular, have been reported to metastasize to the breast and appear as IBC (Gonzalez et al., 2016).

To our knowledge, this is the second reported case of metastatic cervical adenocarcinoma presenting as IBC. Four additional cases of metastatic cervical squamous cell and adenosquamous carcinoma presenting as IBC have previously been reported (Table 1). Inflammatory breast cancer is an uncommon disease, accounting for 1–6% of breast cancers diagnosed in the United States (Yamauchi et al., 2012). Contrary to its name, the disease is caused by tumour cell emboli obstructing dermal lymphatic drainage in the skin of the breast rather than inflammatory cell activity. The resulting breast edema, erythema and peau d'orange appearance can be mistaken for an infectious diagnosis such as mastitis, and misdiagnosis is the most common cause of delay in diagnosis and treatment of IBC (Yamauchi et al., 2012). The diagnosis of IBC is clinical in patients with pathologic confirmation of invasive carcinoma and is based on the rapid onset of breast erythema, edema and/or peau d'orange with a duration of less than six months and involving at least one-third of the breast (Yamauchi et al., 2012). The patient described above met all of these criteria. Though she did not have a skin biopsy to assess dermal lymphatic obstruction, the left axillary node involvement was likely obstructing lymphatic drainage of the breast, mimicking IBC.

Ward et al. (1989) previously reported the only other case, to our knowledge, of metastatic cervical adenocarcinoma appearing as IBC. A 48-year-old patient developed sudden onset swollen painful right breast accompanied by erythema and peau d'orange approximately 18 months after diagnosis of FIGO stage IIB, moderately differentiated cervical adenocarcinoma. Breast biopsy revealed adenocarcinoma, and this was determined to be consistent with endocervical origin rather than a new breast primary following histologic review by three independent pathologists. The biopsies also stained positively for CA-125, a marker indicative of gynecologic adenocarcinomas (Ward et al., 1989).

Subsequent cases in which metastatic squamous cell or adenosquamous cervical carcinomas mimicked IBC have all relied on the histologic and immunohistochemical similarities between the original tumour and breast and/or axillary node biopsy tissues for diagnostic confirmation (Sabatier et al., 2012; Gonzalez et al., 2016; Kelley et al., 1991; Alvarez et al., 2012). Histological comparison is perhaps most challenging in the case of cervical adenocarcinoma, given that adenocarcinoma is also the most common pathology in primary breast cancer. Breast biopsies matching a squamous cell or adenosquamous cervical carcinoma may offer more reassurance that the breast tumour is related to the original cervical disease, since these pathologies are rare in the

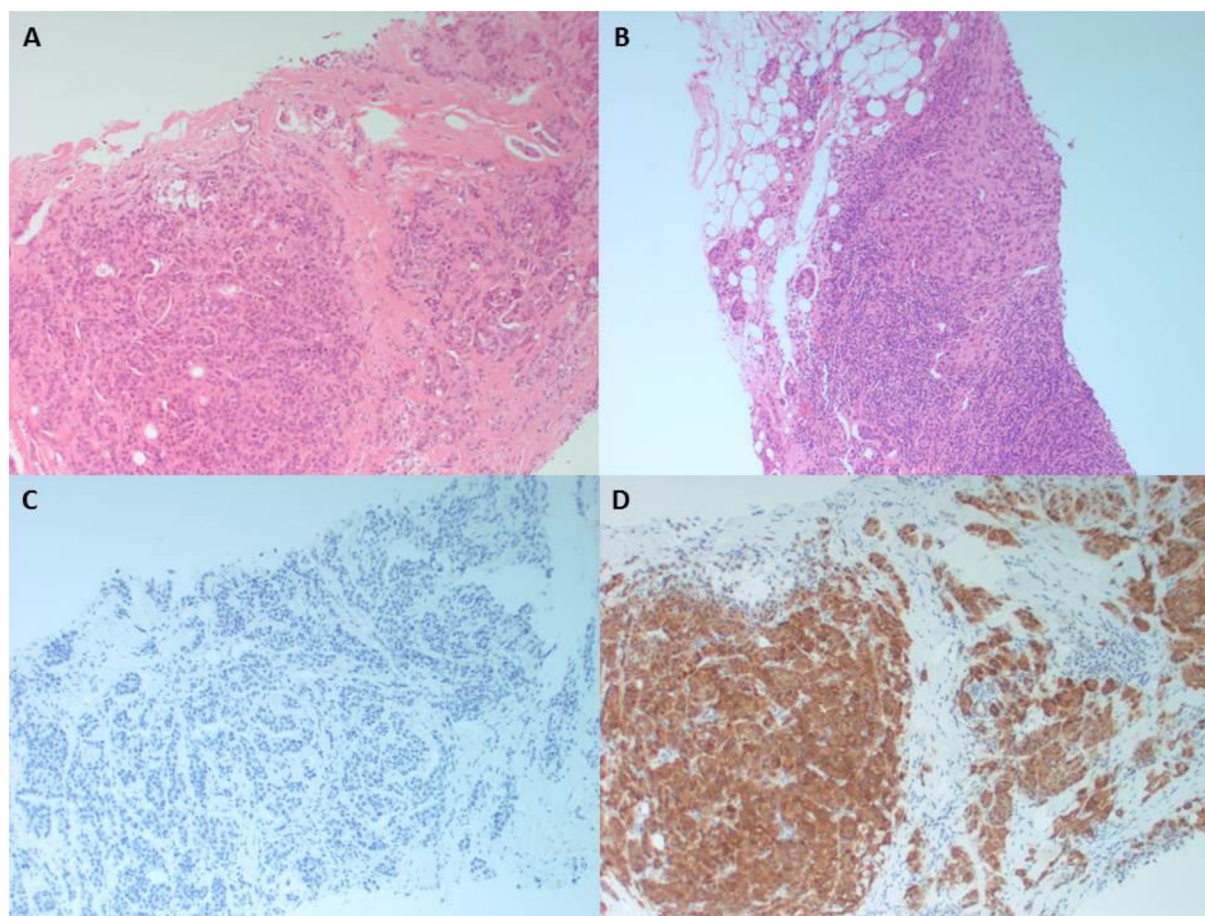


Fig. 2. Breast core biopsy (A, H/E, $\times 100$) showing a high-grade poorly differentiated adenocarcinoma bearing morphological resemblance to the metastatic carcinoma in the left axillary lymph node biopsy (B, H/E, $\times 100$). Immunohistochemical studies were performed on the breast biopsy specimen and showed lack of immunoreactivity for mammoglobin (C) and diffuse positivity for P16 (D).

breast. Positive p16 reactivity, an indicator of HPV-related cancer, has been used to support the diagnosis of metastatic cervical cancer in biopsied breast and axillary node tissues (Sabatier et al., 2012; Gonzalez et al., 2016; Mangla et al., 2017) while negative reactivity for estrogen receptor, progesterone receptor, HER2 and mammoglobin

have helped decrease the likelihood of a second primary breast cancer in previous cervical cancer patients (Gonzalez et al., 2016; Kelley et al., 1991; Mangla et al., 2017).

The case presented was complicated by the patient's comorbid Group B streptococcal bacteremia, with skin thickening and nodal

Table 1

Reports of metastatic cervical carcinoma mimicking inflammatory breast cancer.

Authors	Year	Patient age (years)	Diagnosis	FIGO stage at diagnosis	Location of metastasis	Time to breast metastasis	Diagnostic method	Survival outcome ^a
Ward	1988	48	Adenocarcinoma	IIB	Right axilla and breast	~18 months	● Histology of breast biopsies ● Elevated CA-125	Unknown
Kelley	1991	32	Adenosquamous carcinoma	IB	Left axilla and breast	< 3 months	● Histology of breast and axillary node biopsies ● Negative IHC: ER, PR	Deceased at 1 month
Sabatier	2012	74	Squamous cell carcinoma	IV	Right axilla and breast	17 months	● Histology of breast biopsy ● Positive IHC: P16 ● Negative IHC: CK7	Deceased at 3 months
Alvarez	2012	52	Adenosquamous carcinoma	IIB	Left axilla and breast	~4 years	● Histology of axillary node biopsy	Unknown (hospice)
Gonzalez	2016	35	Squamous cell carcinoma	IIIB	Left axilla and breast	9 months	● Histology of breast and axillary node biopsies ● Positive IHC: P16, P63, CEA, CK7 ● Negative IHC: ER, PR, HER2, GATA-3, mammoglobin ● Elevated CA-125	Deceased at 2 months

^a From time of diagnosis of breast metastasis; CA-125, cancer antigen 125; IHC, immunohistochemistry; P16, cyclin-dependent kinase inhibitor 2A; CK7, cytokeratin 7; P63, tumour protein 63; CEA, carcinoembryonic antigen; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; GATA-3, GATA binding protein 3.

involvement initially thought to be consistent with soft tissue infection. While IBC was considered, the clinical picture and radiographic evidence initially favoured an infection given the rarity of a synchronous malignancy or cervix cancer metastatic to breast. As her breast inflammation worsened despite antibiotic therapy, the diagnosis was revisited with biopsy and imaging consistent with IBC. Careful review of the histology favoured this disease to be related to her original cervical adenocarcinoma.

4. Conclusion

Cervical cancer metastatic to the breast is a rare but significant occurrence that can appear clinically as inflammatory breast cancer. We present the second identified case of a young woman with cervical adenocarcinoma presenting with left breast edema, erythema and peau d'orange. This highlights the necessity of thorough radiological and pathological investigation including histological comparison to the original tumour and molecular markers to differentiate a second primary IBC from metastatic cervical adenocarcinoma.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal on request.

Conflict of interest

The authors declare no conflicts of interest.

Author contributions

DD and LC conceived the idea for the case report. KC and LC wrote

the manuscript. NS provided pathology images and analysis. DD, LC, NS and KC all contributed to the final version of the manuscript. DD supervised the project.

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