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Cervical squamous cell carcinoma metastasis to the breast – A case report from Uganda Cancer Institute

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1. Introduction

Cervical cancer is one of the most common female genital tract malignancies. It remains the second most common cause of cancer death in women between the ages of 20 to 39 years (Siegel et al., 2019). Despite improved strategies in prevention, diagnosis and treatment prognosis remains poor especially in patients with metastatic disease. Metastasis to the pelvis and lungs are common but breast metastasis is very rare. Generally, clinical studies estimate the incidence of non-mammary malignancy metastasizing to the breast to be nearly 0.4 to 3% (Di Bonito et al., 1991). Moreover, distinguishing primary breast malignancy from metastatic deposits remains paramount as it does not only change patient management but also reflects a poor prognosis (Lee, 2007). Histopathology, immunohistochemistry (IHC) and imaging studies play a critical role in evaluation of a breast lump and distinguishing a primary tumor of the breast from a metastatic deposit from an extra mammary malignancy (Lee, 2007). In this case report, we present a patient who was previously treated for cervical cancer and presented months later with a breast mass. Here, we will discuss the challenges in making accurate histopathological diagnosis, the role of IHC staining in narrowing down on definitive diagnosis as in differentiating primary tumor from a metastasis as well as the benefit of having a second or third opinion in revision of histologypathology slides with the sole purpose of making accurate definitive diagnosis and giving appropriate treatment.

2. Case report

The patient was a 27 years old Para 4 + 0 who presented to the gyneoncology clinic with complaint of vagina bleeding about one year. The pertinent associated symptoms were mild pallor and slight weight lost. Past medical, surgical, gynecological history as well as family and social history were unremarkable. On examination, the patient's ECOG performance status was zero (0), there was no fever, no pallor, no jaundice, no dehydration, no edema and lymphadenopathy. The vital signs were in normal limits. The chest and abdominal examinations were unremarkable. Vagina exam showed a 5–6 cm cervical mass involving the upper vagina and parametria, the pelvic sidewalls were free. Digital rectal exam revealed a smooth rectal mucosa. Biopsy and subsequent histology of the cervical mass revealed invasive squamous cell carcinoma poorly differentiated non keratinizing type, as shown in Fig. 1. A final clinical diagnosis of stage IIB cervical cancer was made. Additional work up including abdomenopelvic ultrasound, chest X-ray, complete blood count, liver and kidneys function tests were normal. She was counseled on her diagnosis and modalities of treatment and subsequently treated with concomitant chemoradiotherapy. A once weekly dose of cisplatin was given intravenously at 40 mg/m^2 for five cycles. External beam pelvic radiation (EBRT) was delivered at 2 Gy per fraction with a total of 50 Gy given for 5 to 6 weeks. Pelvic boost of high dose external beam radiotherapy was given 3 weeks later after completion of the initial radiotherapy beacuse brachytherapy was not available at the time.

The patient was lost to follow up and showed up about 6 months later at the surgical oncology clinic complaining of right breast mass. A biopsy and histology of the breast mass revealed invasive ductal carcinoma, with Nottingham grade 3. There was no assessment of the pelvis or pelvic disease documented at the time. The patient was managed by the medical oncology team and completed five cycles of cyclophosphamide, doxirubucin and 5flouro Uracil. Due to progressive disease, the patient was given oral xeloda but showed no improvement. After eight months of progressive disease the patient complained of blood stained vaginal discharge and the gynecologic oncology team review was requested. During our review, the patient had an ECOG performance status of 2, there was a huge breast mass (18 × 16) cm seen involving all quadrants of the right breast that was fungating and necrotic with right axillary lymphadenopathy. The contralateral breast

Abbreviations: SCC, Squamous cell carcinoma; IHC, Immunohistochemistry; EBRT, External Beam Radiotherapy.

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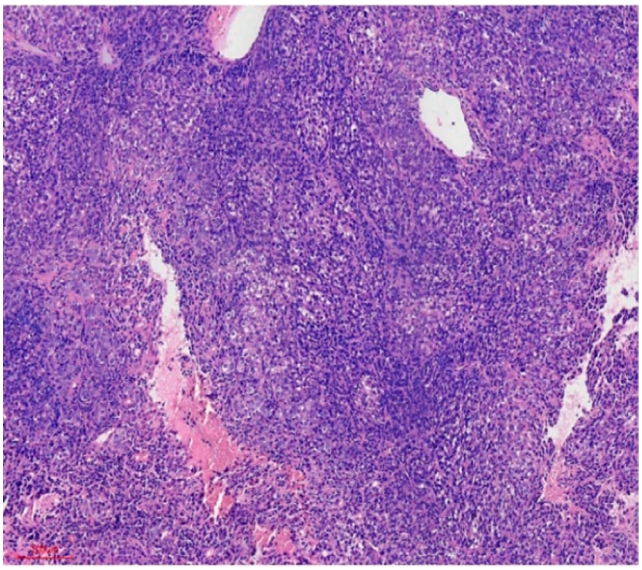

Fig. 1. Histology showing squamous cell carcinoma of cervix.

and other chest examinations were normal. Abdominal exam was unremarkable. Vaginal exam showed endophytic-like lesion on the cervix 2 × 2 cm and fibrosis of the parametria. Digital rectal exam was normal. Chest X-ray showed a huge solid right breast mass but there was no other lesion seen in the lungs field or mediastenum as shown in Fig. 2 below. Histology of the cervical lesion showed invasive poorly differentiated squamous cell carcinoma of the cervix. Due to the progressive nature of the breast mass despite treatment over 8 months by the medical oncology team, the team decided to do a slide review of the initial breast histology specimen that reported invasive ductal carcinoma of the breast by two (one local and one international) pathologists. Both pathologists reported squamous cell carcinoma of the breast as seen in Fig. 3, unlike the initial histology of invasive ductal carcinoma. In addition, immuno histochemistry IHC staining of the specimen for the breast tissue was negative for estrogen receptor, progesterone receptor, and HER2 receptors and had greater than 95% immunoreactive KI-67 and strongly positive for P16. A final diagnosis of recurrent or persistent carcinoma of the cervix with metastasis to the breast was made.

3. Discussion

Almost all patients with metastasis to the breast present with breast

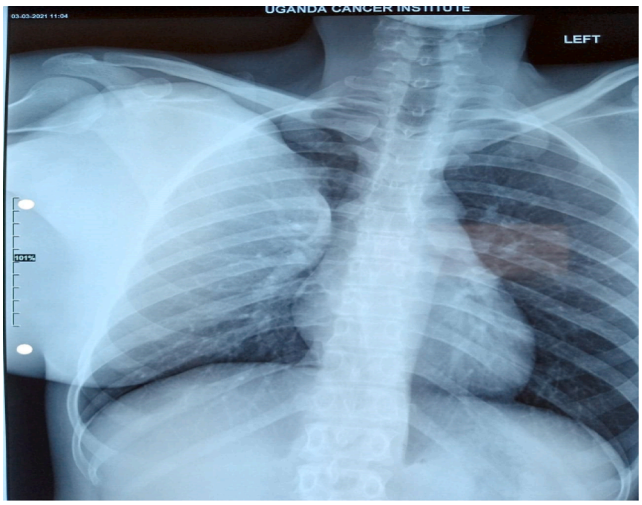

Fig. 2. Chest X-Ray showing huge right breast mass.

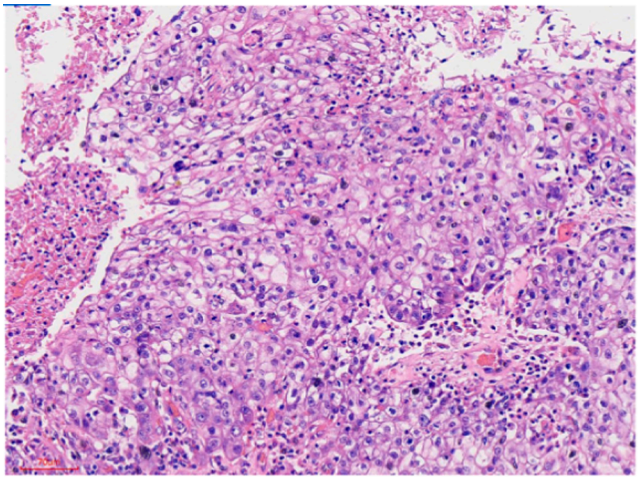

Fig. 3. Breast mass histology showing squamous cell carcinoma.

lump or mass and it is very difficult to distinguish between a primary breast tumor and a metastasis based solely on clinical presentation and histology (Bartella et al., 2003). Primary squamous cell carcinoma of the breast is one of the least common types of breast cancer, and fewer than 25 cases have been reported in the literature (Kwak, 2018). Cancers such as lymphoma soft tissue sarcoma lungs and ovarian cancers as well as Melanoma and gastro-intestinal and genitourinary malignancies are known to metastasize to the breast (Akçay, 2002). Meanwhile, cervical cancer metastasizing to the breast is rare.

In the very few cases of cervical cancer with metastasis to the breast that have been reported, more than 50% had a histology of squamous cell carcinoma with few having adenocarcinoma, adenosquamous carcinoma and small cell carcinoma (Kwak, 2018; Ankit, 2017). This was similar for our patient with the histology of the cervical lesion being squamous cell carcinoma. There is no consistent data on clinical presentation with patients in previous studies presenting with unilateral breast lump or mass (Ankit, 2017). The time interval between diagnosis and treatment of cervical cancer versus appearance of the breast mass usually takes 0 to 9 years. Our patient had a metastatic unilateral right breast mass that was diagnosed 8 months after the diagnosis of the primary tumor of cervical cancer. Various reports have given different time of diagnosis with some diagnosed at initial visit when the patients presented with either a gynecological condition and clinical exam later discover the breast mass with diagnosis of cervical cancer with metastasis to the breast being made concomitantly. Other studies report patients returning with symptoms of cervical cancer recurrences after initial treatment and examination reveals breast mass which turns out to be a metastasis. Others report patients presenting directly with breast symptoms (Kwak, 2018; Ankit, 2017). Although we could not establish whether our patient had persistent or recurrent cervical cancer due to loss to follow up, however, loss to follow-up might suggest that there was remission. It was the breast mass that brought her to the surgical clinic 8 months later after initial treatment by the team. In addition, throughout the period of management for the initial diagnosis of invasive ductal carcinoma of the breast, The patient reported no gynecological symptoms. It was after over a period of another 6 months that the patient started to experience vaginal discharge and alerted the medical oncology team who later referred her to us for review.

3.1. The challenge of accurate histopathologic diagnosis and the role of immnohistochemistry

Accurate histological diagnosis is essential in oncology. Medical errors including pathological diagnostic errors are associated with poor patient outcomes. (Dunn et al., 2005; Leape et al., 1991) It also has the capacity to generate profound diagnostic confusion. This occurred in the

patient where erroneous diagnosis of invasive ductal carcinoma of the breast was made, meanwhile not only did the patient receive inappropriate management but the disease rapidly progressed consequently with a poor prognosis. Secondly, histopathology report is subjective as well as less accurate in differentiating primary breast tumor from metastases (RM et al., 1995; Georgiannos et al., 2001). Hence the use of IHC staining plays an essential role in reaching diagnosis (Klingen et al., 2009). Primary breast SCC demonstrates immunoreactivity for neuron-specific enolase (NSE), E-cadherin, thyroid transcription factor-1 (TTF-1), bcl-2, synaptophysin, and chromogranin. Primary SCC of the breast is also characteristically CK-7 positive and CK-20 negative (Samli et al., 2000). Likewise, P16 is associated with high risk human papilloma virus (HPV) (the causative agent of cervical cancer) and is not seen in normal cervical epithelium (Nam et al., 2007). Together with Ki-67, it is useful in diagnosing small high grade cervical intra-epithelial neoplastic (CIN) lesions.***[17] Estrogen and progesterone receptors as well as Carcinoembryonic antigen (CEA) can be use to detect cancers of ovarian origin (McCluggage, 2007). In this patient, review of the histology slides of the breast mass (which initially diagnosed invasive ductal carcinoma) by the local and international pathologists revealed squamous cell carcinoma. Further IHC staining of the slide was strongly reactive for Ki-67 and strongly positive for P 16. This confirmed diagnosis for us and we concluded with certainty that the squamous cell carcinoima of the breast was just a metastasis of the squamous cell carcinoma of the cervix which is the primary tumor. Estrogen receptors and progesterone receptors were negative in this patient. However, we were not able to do some markers for primary squamous of the breast such as the ones listed above due to limited resources.

4. Conclusion

Cervical cancer metastasizing to the breast is rare. Gynecological examination remains key in a patient who presents with a breast mass, especially who had a recent diagnosis of gynecological cancer. The subjectivity of pathology report coupled with the difficulty in establishing the primary tumor makes IHC staining pivotal in establishing final diagnosis. It is imperative to distinguish a primary breast tumor from a metastatic deposit as it does not only change treatment of the patient, but also predicts a poor prognosis that can be used for counseling.

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

Authors' Contribution

Dr. Deazee M. Saywon formulated the idea for the publication of this case as well as proffering the method, investigating or researching for evidences and compiling of the original draft work of this paper.

Dr. Pius Mulamira was instrumental in providing supervision as well as doing a critical review of this paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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