Abstract
Cutaneous metastasis (CM) from internal malignancies is commonly seen. Sometimes, skin metastases can be the first sign of advanced cancer or an indicator of cancer recurrence. Cases of breast cancer with cutaneous progression after or during trastuzumab therapy have been described in the past, frequently associated with systemic disease progression. However, CM during adjuvant trastuzumab therapy is very rare. It has been hypothesized that cancer cells located in the skin survive and take proliferative advantage by virtue of an immune-tolerance mechanism that hampers trastuzumab-mediated antibody-dependent cell-mediated cytotoxicity. We describe a case of human epidermal growth factor receptor-2-overexpressing breast cancer presenting with diffuse CM during adjuvant trastuzumab therapy.

Key Words: Breast cancer, cutaneous metastasis, human epidermal growth factor receptor-2, trastuzumab

Introduction
Cutaneous metastasis (CM) from internal malignancies is common. CM from solid cancers occurs in about 1% of cases. This incidence is about 2.5% in carcinoma breast patients. However, because of the relatively high incidence of breast cancers, it accounts for almost 33% of CM. Cases of cutaneous progression after or during trastuzumab therapy have been described in the past and are frequently associated with systemic disease progression. This supports the hypothesis by Graziano et al. that cancer cells located in the skin would survive and take proliferative advantage by virtue of an immune-tolerance mechanism that hampers trastuzumab-mediated antibody-dependent cell-mediated cytotoxicity (ADCC). Here, we present one such case of human epidermal growth factor receptor-2 (HER2)-positive locally advanced breast cancer which progressed on adjuvant trastuzumab, first with CM and then systemic spread.

Case Report
A 60-year-old postmenopausal woman presented in December 2014 with a right breast lump. There were no other comorbidities. Core needle biopsy from the lump on histopathological examination (HPE) revealed invasive ductal carcinoma, no specific type, and Nottingham score 3. Immunohistochemistry for molecular biomarkers showed negative estrogen receptor and progesterone receptor with Allred score of 0/8 for each. HER2 was positive (3+) and Ki-67 index was 50%. Positron emission tomography–computed tomography (PET-CT) showed a fluorodeoxyglucose (FDG)-avid 3.6 cm × 3.5 cm × 2.5 cm (maximum standardized uptake value [SUVmax]: 10.8) right upper outer quadrant breast lesion with overlying skin thickening (SUVmax: 3.5) along with level one axillary lymph node 1.4 cm (SUVmax: 3.7) - clinically a cT4N1M0 disease. For this, she received four cycles of dose-dense anthracycline and cyclophosphamide followed by four cycles of 3 weekly taxane (docetaxel) with trastuzumab.

On completion of neoadjuvant chemotherapy, PET-CT showed a reduced size and avidity of the lesion...
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(2.9 cm × 5.4 cm) with overlying skin infiltration. She then underwent right mastectomy and histopathological examination (HPE) showed residual microscopic foci of ductal carcinoma with lymphovascular invasion and uninvolved ipsilateral axillary lymph nodes (00/14). Postsurgery, the patient was given 50.4 Gy in 28 fractions’ radiotherapy (RT) to chest wall and nodal regions, followed by 5.4 Gy in 3 fractions’ local electron boost to by image-guided radiation therapy (IGRT). She tolerated RT well except Grade 2 skin reactions at the end of treatment. Adjuvant trastuzumab was continued every 3 weeks. In March 2016, post 15th dose of adjuvant trastuzumab, she started developing diffuse erythematous rash over the right chest wall, supraclavicular fossa, and right arm within and outside the radiation field. As she was suspected to have radiation recall, adjuvant treatment was put on hold. This was treated symptomatically after dermatologist review. Initially, lesions improved with local treatment, analgesics, and supportive care. Adjuvant treatment was resumed, and two more cycles were given. On follow-up, she was found to have persistent and progressive skin lesions [Figure 1] with a palpable right cervical, level 2 lymph node. There was no evidence of local lesion clinically or radiologically. Biopsy from anterior chest wall skin lesion showed metastatic carcinoma with molecular profile similar to primary breast tumor [Figure 2] and Ki-67 index of 65%. She defaulted on follow-up and took alternative ayurvedic medicines. Seven months later, she came back with extensive skin lesions over the ipsilateral arm and anterior chest wall and progressive dyspnea. Workup with PET-CT revealed disease progression in the form of FDG-avid metastatic skin lesions, cervical lymph nodes, and pleural effusion [Figure 3]. She was started on trastuzumab emtansine (Kadcyla) 3.6 mg/kg every 3 weeks, and since then, the disease was showing partial response to the therapy.

Discussion

Skin metastases though uncommon can be the first sign of advanced cancer or an indicator of cancer recurrence. Our case presented with diffuse CM from HER2-overexpressing breast cancer occurring during adjuvant trastuzumab therapy. Pathogenesis of skin metastasis is suggested to be through tumor cells reaching the dermis through several routes such as contiguous invasion or embolization through lymphatics and blood vessels as well as accidental implantation at the time of surgery. Clinically, various patterns of CM are seen like skin nodule which is the most common presentation and relatively less commonly ulcers. Rarely, erythematous patches or plaques can be seen. The CM may also mimic benign dermatologic lesions such as erythema annulare, contact dermatitis, tinea infections, erysipelas, cellulitis, or cutaneous mucinosis. Most skin metastases from solid cancers are associated with advanced stage of cancer, whereas CM of carcinoma breast can arise in locally advanced disease or in early metastatic phase of the disease. CM patterns in breast cancer vary with the molecular subtypes, and diffuse cutaneous metastases without distant spread have been reported in HER2-amplified disease.

Most of the CMs appear as direct contiguous lesions in relation with the breast primary. Noncontiguous diffuse CMs are almost always seen in advanced disease with systemic spread. Such a condition is very difficult to manage even with multimodality treatment in the form of surgery, RT, chemotherapy, and targeted treatment. Published data suggest that CM from HER-2-overexpressed

![Figure 1](image1.png)

**Figure 1:** Multiple erythematous papules and few hemorrhagic vesicles with excoriation over the right arm

![Figure 2](image2.png)

**Figure 2:** Skin metastasis, tumor emboli, and HER2 expression. (a) Metastatic deposits in superficial dermis (×100), (b) lymphovascular tumor embolus in deep dermis (×400), (c) positive HER2 (3+) in skin metastasis; strong complete membranous staining >10% tumor cells (×200)
breast cancer is seen in early stages of systemic spread, as was seen in our patient. Usual pattern identified in the HER2-positive CM is initial response to the targeted therapy which is followed by flare-up while on treatment.

In patients on HER2-targeted therapy, the concept of “immune privilege” in CM has been suggested, the exact mechanisms of which remain unclear, but it may be due to lack of major histocompatibility complex (MHC) Class II expression in antigen-presenting cells, resulting in impaired immune function in the inferior portions of hair follicles.\cite{5} This can possibly result in immune-tolerance mechanism that hampers trastuzumab-mediated ADCC, as hypothesized by Graziano et al.\cite{5} They suggested that a change occurred in the cutaneous microenvironment of cancer cells leading to the establishment of a “sanctuary-like site” where tumor cells could easily escape from anti-HER2-directed antibodies resulting in the development of CM. Eventually, other possible mechanisms\cite{7} for trastuzumab resistance set in and systemic spread manifests. Further research in this direction can help in developing newer strategies to alter the disease course and reduce the incidence of CM in HER2-positive patients.

**Conclusion**

CM in HER2-positive breast cancer can show initial response to therapy followed by progression on targeted therapy, due to resistance. This can be the early sign of systemic spread; therefore, physicians should perform a detailed physical examination including that of skin even during adjuvant trastuzumab therapy. This will help in identifying these patients for appropriate therapeutic intervention. Skin as a sanctuary site for metastatic tumor cells in HER2-amplified breast cancer appears to be a promising hypothesis and requires further research and validation.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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