Trastuzumab Induced Maculopapular Skin Reactions Localized on the Left Forearm and Arm: A Case Report

Sol Ön Kol ve Kolda Lokalize, Trastuzumab ile İlişkili Makülopapüler Deri Reaksiyonu

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Geliş Tarihi/*Received:* 06.05.2008
Kabul Tarihi/*Accepted:* 27.08.2008

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ABSTRACT Trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER-2 protein, either alone or in combination with chemotherapy, improves the outcome of women with early and metastatic breast cancer. Adverse events including cardiac dysfunction and infusion reactions may develop during trastuzumab therapy. However, skin toxicities are infrequent. We described a 57-year-old woman who was treated with trastuzumab for metastatic breast cancer. Due to the peripheral vein problems experienced by the patient, an implanted central venous access port was placed for the trastuzumab treatment by accessing the left subclavian vein with the distal tip in the mid-superior vena cava. The unusual finding appearing after trastuzumab treatment was the maculopapular rash, which was limited to the left arm and forearm. The patient underwent skin biopsy and pathological examination of specimen showed fixed drug eruptions. We reported this case because drug eruptions due to the trastuzumab treatment are rare and the lesion was only localized to the left arm and forearm of the mastectomy side and port catheter.

Key Words: Breast neoplasm; trastuzumab; skin; drug toxicity

ÖZET Trastuzumab, HER2 proteinini hedefleyen, tek başına ya da kemoterapi ile birlikte kullanıldığında erken evre veya metastatik meme kanserinde sağkalıma etkisi olan monoklonal bir antikordur. Trastuzumab tedavisinden sonra kardiyak disfonksiyonu ve infüzyon reaksiyonlarını içeren yan etkiler görülebilir. Fakat deri toksisitesi sık değildir. Bu çalışmada, 57 yaşında, metastatik meme kanseri tedavisinde trastuzumab kullanılan bir olgu sunulmaktadır. Periferik ven problemi olan hastaya trastuzumab tedavisi için sol subklaviyan vene santral port kateter takıldı. Olgu daha önce sol modifiye radikal mastektomi operasyonu geçirmişti. Olguda trastuzumab tedavisi sonrasında yalnızca sol ön kol ve kolda sınırlı makülopapüler döküntü saptandı. Olgumuzun deri lezyonları biyopsi ile değerlendirildi. Patolojik inceleme sonrasında ilaç erüpsiyonu tanısı konuldu. Trastuzumab tedavisine bağlı deri toksisitesinin nadir olması ve olguda sadece kateterin ve operasyonun olduğu taraftaki kolda lezyonun görülmesi nedeni ile olgunun sunulmasına karar verildi.

Anahtar Kelimeler: Meme kanseri, trastuzumab, deri, ilaç toksisitesi

Turkiye Klinikleri J Med Sci 2009;29(6):1743-6

HER-2/neu proto-oncogene is a poor prognostic factor and is amplified in 20-30% of patients with primary breast cancer. Trastuzumab, a monoclonal antibody (mAb) directed against epidermal growth factor receptor 2 (HER2), improves response, time to progression, and overall survival in both metastatic and adjuvant settings in patients with HER2 positive breast cancer.[1,2] It is well-tolerated but associated cardiotoxicity makes its use problematic with anthracyclines and in patients with cardiac dysfunction.[3] Although other adverse events including fatigue, pne-

umonitis, infusion reactions such as chills, fever, and pain have been reported with trastuzumab therapy, skin toxicity is a rare clinical finding.[4-6] Here we report a 57 year-old woman with metastatic breast cancer who presented with skin reactions that were localized on the left arm and forearm, after trastuzumab treatment.

CASE REPORT

A-57 year-old woman was admitted to our hospital with a mass in her left breast in May 2005. Mammography showed the features of a typical breast cancer and fine needle aspiration cytology (FNAC) suggested an invasive ductal carcinoma of breast. To exclude any metastatic site, chest, abdomen, and pelvis were scanned by computerized tomography (CT) and no metastases were found. Isotopic bone scan results were also normal. The patient was taken to the operating room with a preoperative diagnosis of breast carcinoma and she was treated by left modified radical mastectomy and axillary dissection. Pathological examination of the specimen showed that tumor was invasive ductal carcinoma and invasive lobular carcinoma with axillary lymph node metastases in 8 of 11. Immunohistochemically, the tumor cells were negative for estrogen receptor (ER), progesterone receptor (PR), and 3+ for Her-2/neu. Postoperatively, the patient was given adjuvant chemotherapy including 4 courses of adriamycin and cyclophosphamide (AC), administered at 2 weeks intervals with granulocyte colony stimulating factor (G-CSF) supplementation, followed by 4 courses of paclitaxel, given at 2 weeks intervals with G-CSF supplementation. She was also treated with adjuvant radiotherapy after completion of adjuvant chemotherapy.

After 5 months from the completion of adjuvant treatment, the patient presented to our hospital with a lump in the neck. Examination revealed a mass in the left upper third of the neck, measuring 2 × 2 cm. Excisionel biopsy examination of the mass lesion revealed cervical lymph node metastasis of the breast carcinoma. Immunohistochemically, the tumor cells were negative for ER, PR, and 2+ for Her-2/neu. Fluoro insitu hybridisation (FISH) test was done in order to confirm HER2/neu positivity and tumor was found positive for HER2/neu oncogene. Trastuzumab monotherapy was chosen as the first-line treatment because no visceral metastasis was defined. Due to peripheral vein problems experienced by the patient, an implanted central venous access port was placed for the trastuzumab treatment by accessing the left subclavian vein with the distal tip in the mid-superior vena cava. Trastuzumab monotherapy was started as a single agent with a loading dose of 8 mg per kilogram of body weight and for maintenance therapy 6 mg per kilogram given at three-week intervals. After three courses of trastuzumab therapy, patient presented to our hospital with maculopapular skin reactions localized on the left forearm and arm (Figure 1). Trastuzumab therapy was stopped and the patient was evaluated by a dermatologist in our hospital. Skin reactions improved with local topical treatment (Figure 2). After resolution of skin changes, the dose of trastuzumab was reduced to 2 mg per kilogram and the drug was administered as a single agent weekly. After the second cycle of therapy, localized skin reactions were observed on the same area. Trastuzumab therapy was stopped once again. Topical dermatologic treatment was used. After the recovery of skin reactions, trastuzumab therapy was reintroduced. However, after the fourth cycle of therapy, localized skin reactions recurred. Trastuzumab therapy was stopped again and according to the recommendations of the dermatologist, a skin biopsy was performed. Pathological examination revealed fixed drug eruptions (Figure 3). Trastuzumab treatment was completely stopped and the patient was treated with another chemotherapy protocol including docetaxel and capecitabine.

DISCUSSION

Trastuzumab, a mAb against HER2, improves survival of overexpressing HER2 metastatic and locoregional breast cancer.[1,6] Trastuzumab is generally well tolerated. Infusion-related reactions, mainly during the first infusion and reversible cardiotoxicity are the most frequent adverse events.[3] Skin toxicity is a very rare adverse event with trastuzumab therapy. Here, we described a 57-year old woman

with metastatic breast cancer who presented with skin reaction localized to the forearm and arm associated with trastuzumab therapy. The reactions were severe enough to stop the trastuzumab therapy. As soon as trastuzumab therapy was restarted, skin reaction recurred.

Skin toxicities are the most common toxicity associated with epidermal growth factor receptor (HER1/EGFR) targeted therapies such as mAbs (cetuximab, pantimumab) and oral small molecules (gefitinib, erlotinib). Although the exact role of HER1/EGFR in the skin is not clear, the most common skin toxicity associated with HER1/EGFR targeted therapy is acneiform eruptions, with an incidence of 45-100%.[7-11] Expression of HER1/EGFR has been shown in the skin especially in the epidermis, sebaceous epithelium, ecrine epithelium, and dendritic antigen presenting cells. These areas are potential targets of HER1/EGFR blockades.[12-15] Laux and colleagues reported that skin rash developed with HER1/EGFR targeted therapy but not with HER2 targeted therapy. They also reported that EGFR homodimers were the predominant isoform in human keratinocytes but little or no HER2 heterodimers were found.[16] By contrast, Marques and colleagues demonstrated that the human keratinocyte cell line, HaCaT, expressed EGFR, ErbB2, and ErbB3 and that all three receptors might heterodimerise in all possible combinations.[17] Expression of HER2 in human skin has been reported and it has been shown to have a link to epidermal differentiation.[18] HER1/EGFR plays a key role during keratinocyte proliferation while HER2 is more important during the differentiation process.[19] The skin reactions observed in our patient

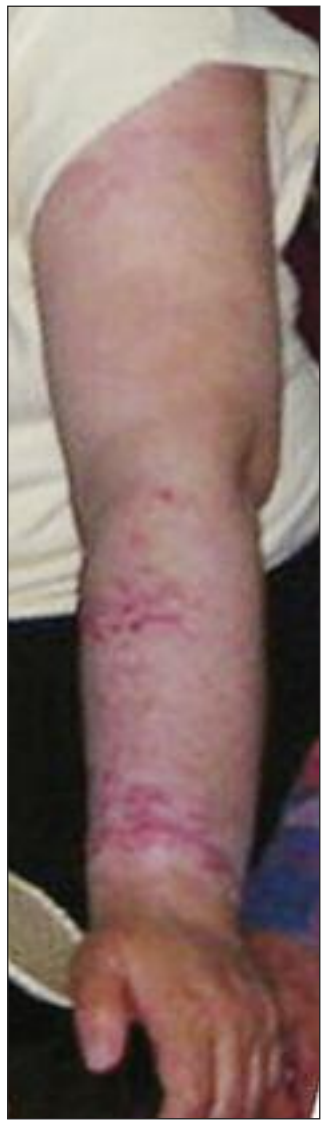

FIGURE 1: Maculopapular skin reaction.

FIGURE 2: Skin reactions improved after local therapy.

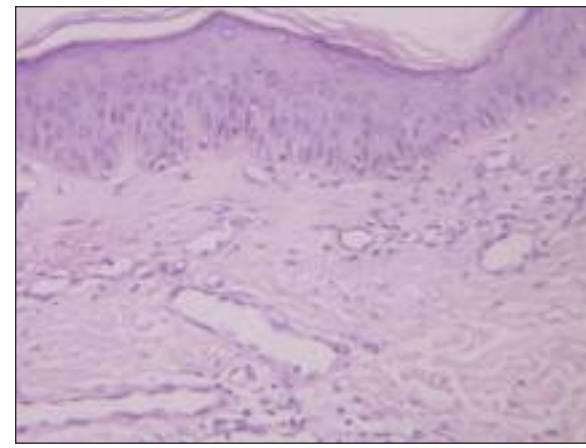

FIGURE 3: Hydropic degeneration of the basal layer, superficial dermal vascular proliferation, mixed inflammatory infiltrate with melanine containing macrophage (HE, x 20).

may be due to inhibition of heterodimerisation of EGFR and HER2 by trastuzumab, just like the typical acneiform like skin reactions seen with HER1/EGFR blockades. Topical treatment has been recommended for acneiform rash occuring after HER1/EGFR targeted therapy.[20] We used topical treatment for the skin reaction of our patient. This kind of skin reactions occurring in patients could be misdiagnosed for infection, thrombophlebitis or skin metastasis. The localization of the skin lesions on the left arm and forearm on the same side of mastectomy operation and port catheter could be attributed to the diminished lenfatic drainage due to axillary dissection resulting in longer trastuzumab exposure leading to such reactions.

In conclusion, treatment with trastuzumab, a mAb against EGFR 2 (HER2), may be a reason for skin toxicity as in HER1/EGFR targeted therapy. Further studies are needed to confirm these results.

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