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Case Review

Breast Cancer En Cuirasses Presentation: Musings of a Clinical Scientist

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Abstract

Breast cancer en cuirasses are an uncommon presentation of metastatic breast cancer. It has no uniform recommendation for treatment. The presentation is not usually alone but is part of more widespread disease. This peculiar pattern of metastatic disease could be a window to unique molecular aspects of metastatic cancer.

INTRODUCTION

Infiltrating ductal breast cancer typically metastasizes to bone, liver, lymph nodes, pleura, lung and brain. ER positive cancer typically favors bone, lung and pleura. TNBC and HER-2 neu over-expressed disease favors brain and liver as well. Skin metastases from breast cancer are distinctly uncommon [1]. T4a lesions, inflammatory breast cancer, long neglected breast cancer and en cuirasses breast cancer are not common but represent unique challenges therapeutically due to the involvement of the skin.

Inflammatory breast cancer is defined by the clinical appearance of the breast not by pathological analysis of biopsy material. The dermal portion of the skin is edematous, peaud'orange, and erythematous, erysipeloid, covering over a third of the breast in a short period of time. Pathologically breast cancer cells are found in dermal lymphatics of the involved skin of the breast. Inflammatory breast cancer is very aggressive. Long neglected breast cancers will involve the skin but pathologically the microscopic appearance is quite different, and the pace of disease progression is much slower [2].

Skin metastases from breast cancer may appear as one or more cutaneous nodules often with erythema. Untreated there is progressive invasion of the skin with retraction and ulceration. En cuirasses are typically diffuse, nodular and associated with fibrosis. The chest wall becomes constricted and indurated with brawny, irregular skin, which may later ulcerate as the cancer progresses [1].

MATERIALS AND METHODS

Clinical experience and extensive literature review are the basis for this paper [3-6]. The methods and materials for the case reported have been published elsewhere [6]. The patient case for our review started in 4/2014 when she was diagnosed with a T4aN3aM0 HER-2-neu overexpressing infiltrating ductal carcinoma of the left breast. She received adjuvant AC followed by TH and external beam radiation treatment. Going forward lymphedema was the only notable adverse event. Recurrent disease was detected on 7/2016 on the right breast with a palpable 6.3 cm mass.

She received 4 cycles of TAC in Mexico. She did not complete recommended treatments and returned to the USA for ongoing care. A follow up MRI of right breast in 3/2017 confirmed refractory disease and she was started on THP. A right mastectomy done revealing a T4bN1aM0 HER-2.neu overexpressing infiltrating ductal carcinoma. Treatment response in breast was only a PR (6.3 cm to 3 cm). Follow up response to treatment imaging on January 25th, 2019, revealed one brain metastasis, multiple lung metastases and metastases to the right kidney. Metastatic disease overexpressing Her-2-neu was confirmed by lung biopsy. Skin biopsy done January 30th, 2019, confirmed metastatic breast in diffuse skin presentation. Over the preceding 2 years multiple skin biopsies were non-diagnostic. The patient was then started on capecitabine and Herceptin. She frequently only took capecitabine due to noncompliance. Progressively worsening diffuse skin metastases were noted on December 31st, 2019. Skin metastases were not better in terms of size, number or symptoms such as pain and bleeding, so carboplatin, gemcitabine and Herceptin were ordered 5/2020. Response in visceral sites was marginal but skin metastases progressed unabated. Topical 5-fluorouracil ointment was applied to skin lesions under an occlusive

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dressing but only a PR was noted in terms of size and only a modest reduction in serosanguinous secretions. Electron beam radiation was ordered in view of treatment failures. Skin metastases extended onto scalp, around entire neck, all of torso, left arm and forearm and below the inguinal folds on the right. Radiation controlled some of the torso-based lesions well but left arm and forearm metastases were not controlled. Progression of the skin metastases despite radiation treatment and progression of lung metastases were the primary reasons for staring trastuzumab-deruxtecan, 5.4 mg/kg IV over 90 min days 1 every 21 days. Marked improvement was noted for all skin lesions after 2 cycles of trastuzumab-deruxtecan. Inspection as a means of assessing patient response was quite fascicle since the lesions were raised, palpable, red and oozing serosanguinous fluids.

RESULTS AND DISCUSSION

Skin invasion by breast cancer causing an cuirasses presentation reveals thickening and tightening of the affected area, bleeding and oozing of serosanguinous fluids and pain even if there is no evidence of infection or acute breach of the tissue integrity. The patients might be cared for successfully with surgery for limited lesions. Photon based radiation therapy frequently works initially only to frequently fail. Tissue tolerance limits its repeated use. Chemotherapy may be of benefit but in the case for discussion it is important to note topical 5-fluorouracil failed as did oral capecitabine. Therefore, pharmacokinetic reasons for failure were not the cause for the regimen's failures. Anthracyclines, alkylating agents and taxanes also failed. Anti-Her-2-neu therapies also failed with one exception, trastuzumab-deruxtecan. Whether this was all pharmacodynamically based or not is unknown. Given the limited and disrupted blood supply of skin involved by this type of breast cancer presentation perhaps, subcutaneous formulations of trastuzumab-deruxtecan or trastuzumab with pertuzumab closer to the lesions may well yield equally much improved control of the disease.

Successful treatment of inflammatory breast cancer typically results in a normal appearance of skin over the breast. Successful treatment of en cuirasses metastases leaves the previously affected area with notable atrophy, thinning. No regrowth of hair is seen in these areas. In the case report noted an area also involved by herpes zoster demonstrated loss of muscle as well as dermal fat resulting in a trench like defect. While probably not part of the successful initiation of tumor growth in the skin it highlights the diversity between breast cancer subtypes involving the skin in terms of their interaction with their microenvironment.

The most striking abnormality seen with this type of presentation of metastatic breast cancer is the disease has preferentially grown in an area much colder than the normal body temperature. Inflammatory breast cancer, nodular presentations of melanoma more so than squamous cell carcinoma of the anus, basal cell carcinoma and squamous cell carcinoma of the skin share this odd pattern of growth away from normal body temperatures. Metabolism slows at lower temperatures and normal enzymatic structure as well as function is dependent on normal human body temperature. Some exceptions exist such as normal spermatogenesis requires a lower body temperature. What follows are suggestions for mechanisms that allow breast cancer to produce such an odd anti-thermotropic metastasis.

Transitioning murine breast cancer cells *in vitro* from 98 degrees F to 95 results in more than half the cells dying within hours and the rest dying or not replicating (personal observations). Like heat shock proteins there are cold shock proteins. Cold shock proteins are rapidly produced in response to cold [7,8]. YB-1 in particular affects p53 induced cell death. It also affects cell cycle control [9]. Other cold shock proteins bind Notch-3 proteins and interfere with VEGF expression [10-13]. The cancer cells spreading to the skin must survive and then grow. Perhaps multiple cold shock proteins are involved in the development of en cuirasses metastases.

GC rich areas of DNA or RNA would most likely be the ones most profoundly affected by lower temperatures. In fact, areas of mRNA enriched for low complexity sequences such as GC rich areas are bound preferentially by cold shock proteins. Hairpin loops in RNA would be more stable and low molecular weight RNAs might experience slower metabolism as well. Proteins promoting cell growth could also degrade slower at lower temperatures. The protein nucleic acid complexes formed by cold shock proteins result in stress granule formation. Clearance of these granules may occur via lysosomal mechanisms [14-19]. Trastuzumab-deruxtecan is disassembled in the lysosomes. Its chemotherapeutic payload is thereby released. It is possible that cold shock proteins facilitating en cuirasses metastases also enhanced lysosomal activity thereby enabling the antibody-drug conjugate to successfully control the cancer through enhanced release of the drug from the conjugate compound [20].

CONCLUSION

More questions exist than answers. The crossroads of en cuirasses presentations and inflammatory breast cancer may harbor unique new targets for anticancer treatment. Certainly YB-1 and other cold shock proteins appear to loom large in this presentation of cancer, but considerable basic research is needed in this area. As in the past and on into the future it will be critical to identify the correct target(s) for our best therapeutic agents in breast cancer [21].

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