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Cutaneous Adverse Effects of Hormonal and HER2-Targeted Therapies in Breast Cancer Patients: A Case Series

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ABSTRACT

Background: Aromatase inhibitors (AIs) and anti-HER2 therapies improve breast cancer survival, but dermatologic adverse events (dAEs) are underrecognized despite affecting quality of life and adherence.

Methods: We report 4 cases of cutaneous toxicity from AIs or HER2-targeted agents, detailing presentation, management, and outcomes.

Results: Three patients developed acneiform eruptions: one after starting letrozole, resolving on discontinuation, and 2 on trastuzumab/pertuzumab requiring isotretinoin after failing topical/antibiotic therapy. A fourth developed lichen planus pigmentosus six months into anastrozole chemoprevention, with limited response to topicals and treatment cessation due to psychosocial distress.

Conclusion: Acneiform eruptions may occur with both HER2 blockade and AIs, while pigmentary disorders may represent a novel AI toxicity. Prompt recognition and targeted care may facilitate cancer treatment continuation.

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INTRODUCTION

Endocrine therapy, including aromatase inhibitors (AIs) and tamoxifen, and human epidermal growth factor receptor 2 (HER2)-targeted therapy, have significantly improved breast cancer outcomes, reducing mortality and prolonging disease-free survival.[1-3]

AIs block aromatase-mediated conversion of androgens to estrogens in peripheral tissues, making them particularly effective in postmenopausal women.[4] Commonly used third-generation agents include anastrozole and letrozole (nonsteroidal) and exemestane (steroidal).[3]

Anti-HER2 monoclonal antibodies trastuzumab and pertuzumab downregulate HER2 signaling and induce immune-mediated tumor cell death, and are standard therapy for HER2-overexpressing tumors.[5]

While generally well tolerated, AIs may cause hot flashes, arthralgias, alopecia, pruritus, xerosis, hypersensitivity, vasculitis, and lichenoid eruptions.[6-11] Trastuzumab's common toxicities include diarrhea and dermatitis;[12] but rarer dermatologic adverse events (dAEs) like psoriasis, dermatomyositis, acneiform eruptions, and pigmentary changes are described.[13-19] Despite their implications for treatment adherence and quality of life, dAEs remain poorly characterized.

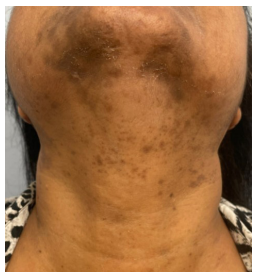
Case 1: A 57-year-old woman with stage IIb ER+/HER2+ breast cancer developed painful papules and pustules on her face days after starting adjuvant letrozole. Topical metronidazole and ketoconazole were ineffective; doxycycline provided little benefit until letrozole was discontinued, after which lesions resolved rapidly.

Case 2: A 40-year-old woman receiving pertuzumab, trastuzumab, and tamoxifen developed inflammatory papules and pustules on the face and neck within 2 weeks (Figure 1). Multiple topical and oral agents failed; isotretinoin achieved near clearance in 5 months without interrupting anti-HER2 therapy.

FIGURE 1. Acneiform eruption with diffuse pustules and papules on the face of a 40-year-old woman shortly after receiving pertuzumab, trastuzumab, and tamoxifen.

FIGURE 2A. Brown-gray macules and patches on the face and neck of a 55-year-old woman after 6 months of anastrozole.

FIGURE 2B. Same patient after several months of topical depigmenting treatment showing moderate improvement.



Case 3: A 38-year-old woman on a HER2 inhibitor trial drug developed facial and truncal acneiform eruptions. Doxycycline provided transient improvement. Worsening occurred with addition of paclitaxel/trastuzumab/pertuzumab. Low-dose isotretinoin and topical steroids led to clearance within 3 months.

Case 4: A 55-year-old woman taking anastrozole for chemoprevention developed progressive brown-gray facial and neck macules after 6 months (Figure 2A). Biopsy suggested lichen planus pigmentosus (LPP). Multiple topical agents yielded modest improvement (Figure 2B); she ultimately discontinued anastrozole due to psychosocial impact.

DISCUSSION

Cutaneous toxicities are common across breast cancer therapies, including chemotherapy, targeted agents, immune checkpoint inhibitors, and hormonal therapy.[17,20-23] This series highlights various dermatologic adverse effects with the use of aromatase inhibitors and anti-HER2 therapy for the treatment of breast cancer.

AIs most often cause alopecia, pruritus, xerosis, and flushing; rarer effects include vasculitis, erythema nodosum, subacute cutaneous lupus erythematosus, and lichenoid eruptions.[6-11] Our series is notable for acneiform eruptions with both AIs and anti-HER2 agents. While anti-HER2–associated acneiform rashes are well documented, they are rarely reported with AIs.[17,21] In Case 1, symptoms arose within days of letrozole initiation and resolved after drug cessation.

Anti-HER2 therapy-induced acneiform eruptions (Cases 2, 3) were persistent and required isotretinoin. Prior reports describe onset within 3 weeks of trastuzumab and response to oral antibiotics or topical steroids, though secondary bacterial infections can occur.[17,24]

The mechanism of HER2-inhibitor-related eruptions is unclear but may parallel EGFR inhibitor-induced toxicity given HER2 and EGFR structural similarity. Disruption of keratinocyte differentiation and induction of apoptosis may underlie these eruptions.[25-28]

Pigmentary disorders are less recognized. Our case of LPP with anastrozole monotherapy appears unique. Tamoxifen has been linked to LPP, possibly via effects on melanogenesis.[29] AIs, through estrogen suppression, may also alter pigment production. Further research is warranted to explore its role in pigmentary alteration, particularly given the psychosocial burden and treatment resistance in our case.

TABLE 1.

Dermatologic Adverse Events (dAEs) in This Series

Drug Class	Agent(s)	Common dAEs	Less Common dAEs	Relevant Case
Aromatase Inhibitors (AIs)	Anastrozole, Letrozole, E xemestane	Alopecia, pruritus, xerosis, flushing	Hypersensitivity, vasculitis, lichenoid eruptions, maculopapular eruptions, erythema nodosum, subacute cutaneous lupus erythematosus	Case 1: Acneiform eruption (Letrozole) Case 4: Lichen planus pigmentosus (Anastrozole)
Anti-HER2	Trastuzumab, Pertuzumab	Acneiform eruption, dermatitis	Psoriasis, dermatomyositis, erythrodysesthesia, carotenoderma	Case 2 & 3: Acneiform eruptions (Trastuzumab/Pertuzumab)

CONCLUSION

We present several cases of cutaneous reactions in patients undergoing treatment with aromatase inhibitors and anti-HER2 therapies. It is important for clinicians to be aware of potential adverse reactions; prompt recognition and appropriate treatment could enable the continued use of oncologic therapies while preserving patients' quality of life.

DISCLOSURES

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