Received: 19 April 2024 | Revised: 28 May 2024 | Accepted: 5 June 2024

DOI: 10.1002/ccr3.9103

CASE REPORT

Clinical Case Reports Open Access WILEY

Trastuzumab-induced toxic epidermal necrolysis in a Her-2-positive metastatic breast cancer patient—A rare case report

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Key Clinical Message

Toxic Epidermal Necrolysis (TEN) is a rare, but potentially fatal mucocutaneous reaction, that may occur due to an immunologic response to certain medications. However, TEN triggered by Trastuzumab is extremely rare. Early diagnosis, recognition, and prompt cessation of the offending drugs and initiation of steroid therapy with supportive management are the most important actions for managing TEN. Although rare, it is important to be vigilant about this potential adverse reactions associated with trastuzumab to ensure patient safety and contribute to better outcomes.

KEYWORDS

anti HER-2 antibody, HER-2-positive breast cancer, Steven Johnson syndrome, toxic epidermal necrolysis, Trastuzumab

1 | INTRODUCTION

Overexpression of human epidermal growth factor receptor 2 (HER-2) occurs in 25%–30% of breast cancer patients.[1] Trastuzumab is a humanized monoclonal antibody that binds to the human epidermal growth factor receptor 2 (HER-2)/neu receptor and has been shown to increase not only overall survival but also disease-free survival in patients with HER-2-positive breast cancer.[2,3]

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) exist as a spectrum of mucocutaneous hypersensitivity reactions with a mortality rate of up to 30%.[4] It is characterized by erythema, necrosis, and bullous detachment of the skin and mucosal membranes. If there is less than 10% epidermal detachment, the diagnosis is SJS, if there is between 10% and 30% involvements of skin, the diagnosis is SJS-TEN overlap syndrome.[5] The more severe TEN designation is used when epidermal detachment is greater than 30%.[6]

SJS/TEN most commonly presents as an adverse drug reaction; however, infectious agents, immunotherapy, and tamoxifen have also been implicated.[7] Approximately 25% of cases are idiopathic.[4] Genetic predisposition in carriers of different human leukocyte antigens (HLA)-B has been demonstrated.[7]

We present a 36-year-old female with a history of HER2-positive left breast cancer with brain metastasis,

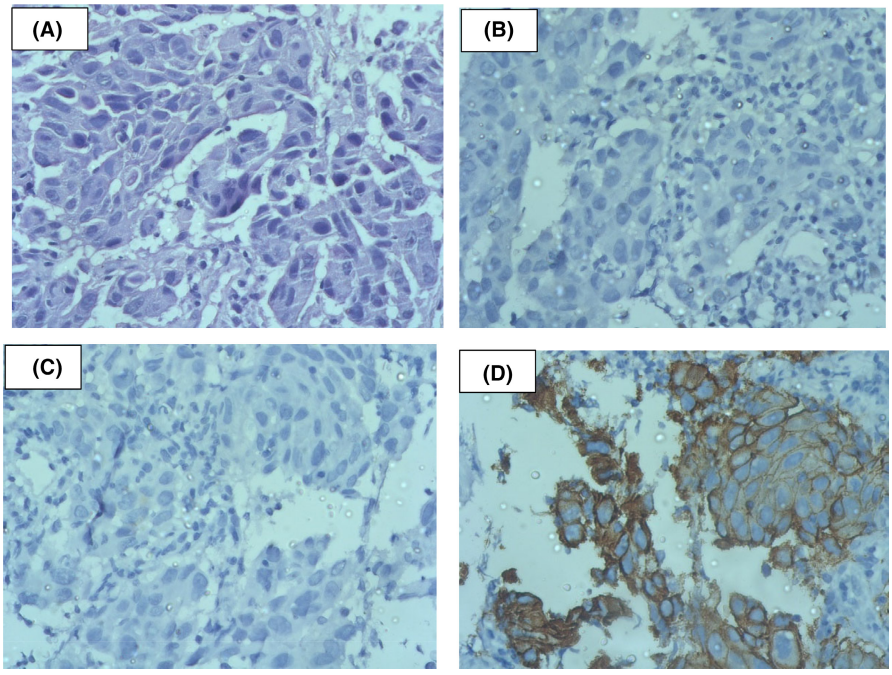

FIGURE 1 Slides showing histopathology and immunohistochemistry. (A) Histopathology slide showing invasive ductal carcinoma, Grade 3; (B) Immunohistochemistry showing all estrogen receptors (ER) negative (magnification 40×); (C) Immunohistochemistry showing all progesterone receptors (PR) negative (magnification 40×); (D) Immunohistochemistry showing HER2 receptors positive (magnification 40×).

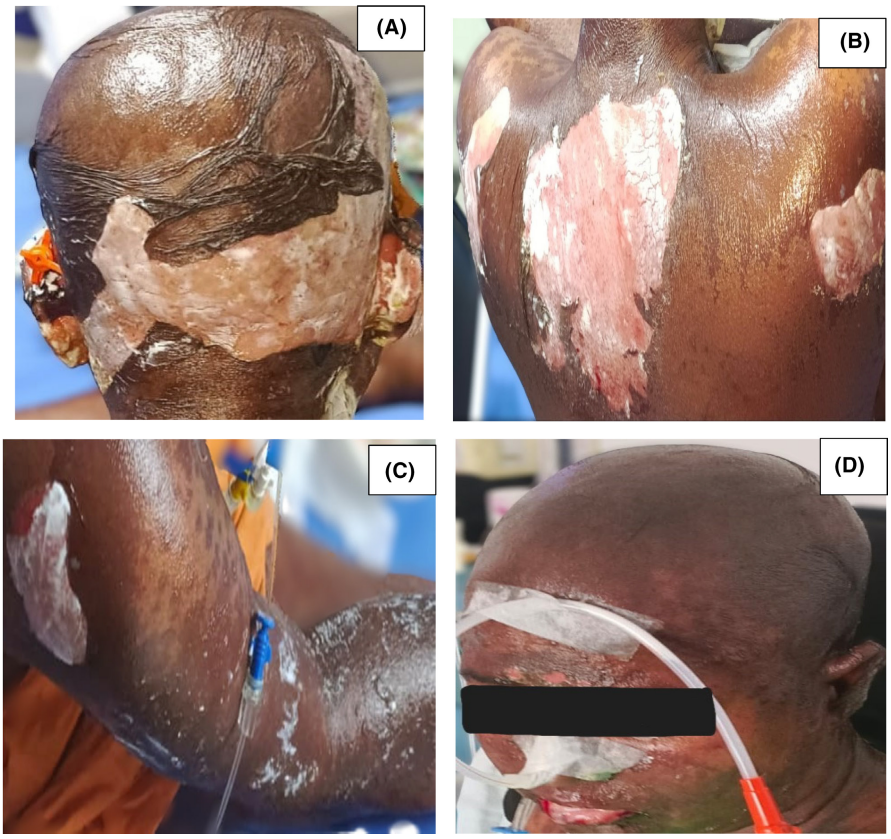

FIGURE 2 Images showing clinical feature of TEN. (A) Showing blister and epidermal detachment of skin on scalp and ear. (B) Showing epidermal detachment over back and shoulder. (C) Showing blister and commencement of epidermal detachment at the skin over arm and forearm. (D) Showing blister over face and commencement of epidermal detachment at the skin over forehead and mucositis over lip.

who developed TEN syndrome after her first dose of trastuzumab.

2 | CASE HISTORY

This is a confirmed case of carcinoma in the right breast, with the spread of cancer cells to the lymph nodes in the right armpit since January 2022. The histology test confirmed the diagnosis of Invasive ductal Carcinoma, Grade III (Figure 1A). The receptor status indicated that the estrogen receptor (ER) was negative (Figure 1B), the progesterone receptor (PR) was negative (Figure 1C), and the human epidermal growth factor receptor 2 (HER-2) was positive (3+) (Figure 1D). The patient had received neoadjuvant chemotherapy, consisting of four cycles of doxorubicin + cyclophosphamide followed by four cycles of docetaxel at 3-week interval. A right-sided modified radical mastectomy surgery followed this, and then loco regional radiotherapy till June 2022. She was advised to undergo Trastuzumab, an anti-HER-2 antibody, but she was unable to afford it. One year later, in June 2023, she presented with brain metastases and underwent whole-brain radiation, receiving a total dose of 30Gy administered in 10 fractions. After finishing radiation, she was recommended to undergo treatment with either Trastuzumab or Tucatinib (anti HER-2 agents) in addition to oral capecitabine.

Nevertheless, she was unable to get it once again because of financial limitations. Hence, we started Lapatinib + capecitabine as palliative therapy. After 1.5 months, the patient consented to receiving Trastuzumab and was administered her first dosage of the medication. Three days post-administration of Trastuzumab, she presented with symptoms including fever, sore throat, odynophagia, and generalized rashes. Based on these grievances, she was admitted to our hospital.

3 | METHODS

After being hospitalized, she had a sudden and intense appearance of painful and itchy blisters on her shoulders, back, abdomen, and scalp. The blisters then spread to her arms, chest, groin, and thighs, eventually leading to the outer layer of her skin. There were areas of denuded skin. The result of Nikolsky's sign was positive (Figure 2A,B).

In addition, she had severe mucositis affecting her eyes, lips, oral cavity, pharynx, and genital area (Figure 2C,D). The estimated extent of body surface area (BSA) affected was 35%.

TABLE 1 SCORTEN (score of toxic epidermal necrosis).

Number of parameters	Predicted mortality
0	1%
1	4%
2	12%
3	32%
4	62%
5	85%
6	95%
7	99%

Note: Parameters: Age > 40 years, malignancy, heart rate > 120 beats/min, epidermal detachment > 10% of body surface area, serum urea > 10 mmol/L, serum glucose: 14 mmol/L, serum bicarbonate < 20 mmol/L.

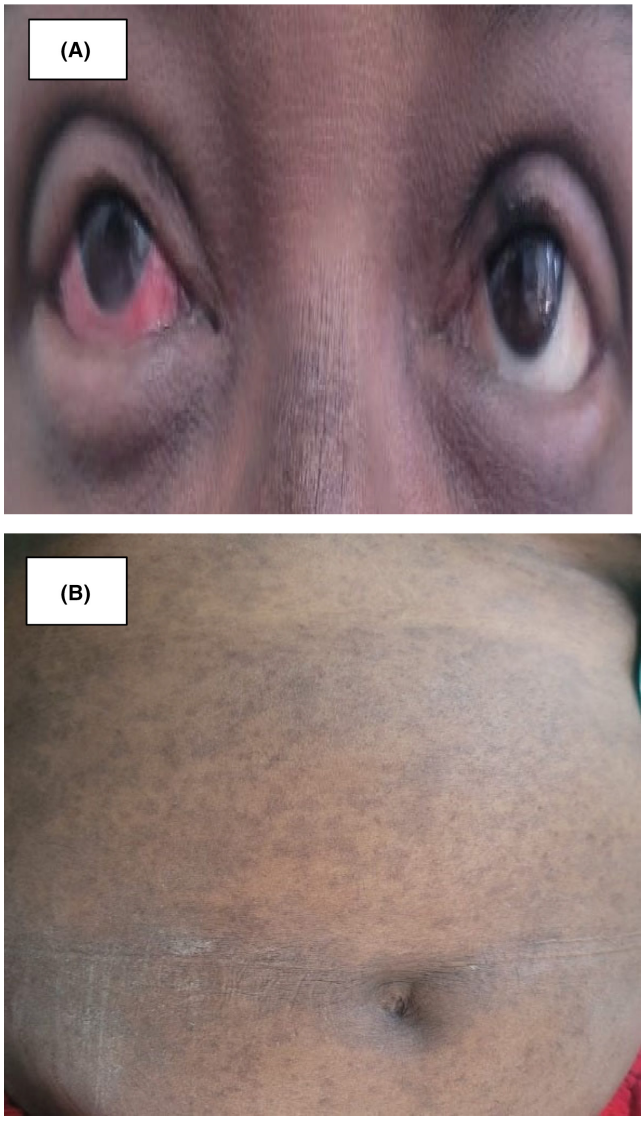

FIGURE 3 (A) Showing conjunctivitis after recovery. (B) Showing dyspigmentation at the skin over the abdomen after recovery.

The complete blood count revealed leukocytosis with a count of 22,000/μL (normal range: 4500-11,000/μL) and a hemoglobin level of 8 g/dL (normal range: 12–16 g/dL). The renal and liver function tests yielded normal results. The C-reactive protein (CRP) level was measured to be 35 mg/L, which is over the recommended limit of <10.0 mg/L. Her heart rate was 100 beats/min. Her serum glucose level and serum Bi carbonate level were within normal range. Due to the fact that the detachment of the outermost layer of her skin was 35% of her body surface area, she was diagnosed with toxic epidermal necrolysis. Her SCORTEN scale score was 2 (Table 1). The patient received supportive management, including the administration of high-dose steroids (methylprednisolone), antihistamines (diphenhydramine), analgesics (Tramadol hydrochloride), antibiotics (piperacillin + Tazobactum 4.5 gm every 6 h), antifungal medication (Caspofungin), fluid and electrolyte replacement, nutritional support through nasogastric feeding, oral care using 1% povidone-iodine mouthwash or benzydamine mouthwash alternatively, local antifungal treatment with 2% miconazole, skin care, eye care, physiotherapy, and psychological support. She saw a steady improvement in her health over a period of 4 weeks. Despite ongoing complications of entropion resulting in frequent conjunctivitis, as well as bronchiectasis and depigmentation leading to a chronic cough, she continues to experience these symptoms (Figure 3A,B). Currently, she is undergoing palliative chemotherapy with the drugs Capecitabine and Lapatinib.

4 | CONCLUSION AND RESULTS

TEN is a rare but serious drug reaction that can have a rapid and fatal course. Early diagnosis, recognition, and stopping the offending drugs immediately while initiating steroid therapy and supportive management are the most crucial actions to take. Patients who experience such side effects should be closely monitored for any lingering sequelae associated with TEN, including cutaneous, ocular, and oral sequelae, all of which can significantly impair the quality of life of cancer patients. It is important to note that this is the only reported case of TEN triggered by Trastuzumab therapy. Oncologists must inform their patients about the potential risks associated with trastuzumab and maintain constant vigilance to ensure their safety.

5 | DISCUSSION

In 1956, Alan Lyell, a Scottish dermatologist, reported the first case of TEN.[8,9] TEN is an extremely rare, acute hypersensitivity reaction involving the skin and mucous membranes. Its incidence is approximately 0.4–1.2 cases per million person/year.[10] Medications are responsible for at least 70% of cases of TEN. Allopurinol, antiepileptics (carbamazepine, lamotrigine, phenobarbital, and phenytoin), nevirapine, oxicam NSAIDs, and antibacterial sulfonamides are the most common drugs causing TEN.[11] Infectious agents have also been implicated, mainly by mycoplasma, herpes simplex virus, and cytomegalovirus.[7] Few cases have been reported following cancer treatments, including vemurafenib, ipilimumab, tamoxifen, nivolumab, and pembrolizumab.[4]

TEN was previously considered to be related to Fas–Fas ligand or granulysin-mediated apoptosis.

More recent studies suggested the reactive oxygen species (ROS) as the initiating factor for keratinocyte damage and that it precedes the activation of the apoptotic systems.

Fas is a membrane-bound protein responsible for the initiation of programmed cell death through a series of intracellular events. Fas ligand (FasL), which is usually produced by cytotoxic T (CTL) cells and natural killer (NK) cells, tends to bind to Fas on target cells, initiating apoptosis. The fact that the number of these cells is low in skin biopsies taken from TEN patients indicates that they are not the source of FasL.[12] Virad et al.'s study in 1998 found a high level of keratinocyte localization of FasL. This suggests that keratinocytes may be responsible for their own death.[13] Granulysin is a pro-apoptotic protein that was also detected in TEN blisters. It is one of many cytotoxic molecules secreted by CTL and NK cells that lead to cell-mediated cytotoxicity.[14]

Oxidative stress is one of the proposed theories of TEN. Glutathione S-transferase-p (GST-p) is a biomarker of oxidative stress in keratinocytes. A higher level of this marker has been detected in TEN patients compared to other cutaneous drug reactions.[15] The culprit drug may interfere with the detoxification pathways resulting in the accumulation of reactive oxygen species (ROS), triggering programmed cell death.[16]

TEN usually presents with a prodrome of fever, malaise, and upper respiratory tract symptoms 7–21 days after the initiation of the causative drug. Features more suggestive of TEN are acute onset and rapid worsening of painful lesions of the skin and mucous membranes, including eyes, mouth, nose, and genitalia. Skin lesions manifest as blisters and ulcerations arising on generalized macules with purpuric centers. The large denuded areas lead to massive loss of fluid and protein, bleeding, hypothermia, and infection. Necrolysis of respiratory and gastrointestinal epithelium can occur and lead to bronchial obstruction and profuse diarrhea. The Nikolsky's sign, which describes the detachment of the epidermis by minimal tangential pressure, is a helpful clinical indicator.[10,17,18]

The prognosis of TEN is assessed based on the SCORTEN scale,[8,10] showing in Table 1.

It is based on seven variables that need to be evaluated within the first 24 h of hospital admission. These variables include age, affected body surface area, heart rate, and presence of malignancy, serum urea, glucose, and bicarbonate.[19]

The mainstay treatment of TEN is supportive care until re-epithelialization of the affected skin. Supportive measures include fluid resuscitation, pain management, wound care, and nutritional support. Early management of these cases in the emergency department should focus mainly on two measures: discontinuation of the offending drug and early referral to a burn unit or intensive care unit with experience in dealing with such cases. When taken in the first 24 h of blister formation, these two measures decrease infection rate and hospital stays and improve overall survival.[20]

The airway should be observed frequently, along with the provision of supplemental oxygen via a face mask if needed. In case of respiratory distress, endotracheal intubation should be done by an expert. Fluid resuscitation using crystalloids should be guided by one of the standard burn resuscitation Performa (e.g., Parkland formula). The target of resuscitation should be to maintain adequate tissue perfusion by achieving an adequate mean arterial blood pressure (ABP > 65 mm Hg), a central venous pressure between 8 and 12 mmHg, and a urine output of 0.5–1 mL/kg/h.[21,22] Pain management is extremely important to decrease a patient's distress. Opiates or patient-controlled analgesia (PCA) can be used. The non-adhesive sterile dressing should be used to dress areas of skin erosions, and care should be taken to prevent hypothermia, especially in the prehospital setting.[20]

Nutritional support is crucial in TEN patients due to the hypercatabolic nature of this disease. Enteral feeding is superior to parenteral feeding as it decreases the risk of bacterial translocation. If oral mucosa is significantly affected, a nasogastric tube may be used. Energy requirements and nutritional support must be carefully calculated (aim to 20–25 kcal/kg/day).[23,24]

Several complications can occur in TEN patients because of the extensive cutaneous and mucosal membrane involvement. In the early stage, the presence of painful stomatitis may interfere with oral intake with an increased risk of dehydration. Loss of the epithelial barrier increases the risk of infection and septicemia. This may evolve into septic shock and multi-organ failures.[25] In the long term, the involved skin may show signs of hypo or hyperpigmentation, while the affected mucosal surfaces may heal by stenosis and strictures. In females, vulvovaginal involvement is common and can lead to stenosis, vulvar adenosis, and dyspareunia. In men, phimosis is the most common complication.[26]

Ocular complications are one of the most common and serious sequelae of TEN. Therefore, early ophthalmological consultation is advisable in such cases. Corneal ulcers, xerophthalmia, meibomian gland dysfunction, panophthamitis, or even blindness are some of the reported complications.[27] Respiratory complications include pulmonary embolism, adult respiratory distress syndrome (ARDS), and pneumonia.[28] Gastrointestinal complications are in the form of extensive bleeding from the affected mucosa, gingival synechia, and xerostomia due to affection of the salivary glands.[29]

AUTHOR CONTRIBUTIONS

Jannatul Ferdause: Conceptualization; data curation; formal analysis; investigation; methodology; supervision; writing – original draft; writing – review and editing. **Sura Jukrup Momtahena:** Data curation; formal analysis; investigation; methodology; resources; validation; writing – original draft; writing – review and editing. **Rubama Karim:** Data curation; formal analysis; investigation; methodology; software; validation; visualization; writing – review and editing. **Aditi Paul Chowdhury:** Data curation; formal analysis; investigation; methodology; resources; software; validation; writing – review and editing. **Nowshin Taslima Hossain:** Data curation; formal analysis; investigation; methodology; resources; software; validation; writing – review and editing. **Md Ariful Islam:** Data curation; formal analysis; investigation; methodology; resources; software; visualization; writing – review and editing. **Maruf Bin Habib:** Data curation; formal analysis; investigation; methodology; resources; validation; visualization; writing – review and editing. **A. K. M. Shafiul Kadir:** Data curation; formal analysis; investigation; methodology; resources; software; visualization; writing – review and editing. **Md Ariful Haque:** Formal analysis; investigation; methodology; resources; software; visualization; writing – original draft; writing – review and editing.

ACKNOWLEDGMENTS

The authors have nothing to report.

FUNDING INFORMATION

Authors have not received any funds.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no financial conflict of interest with regard to the content of this report.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

None.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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How to cite this article: Ferdause J, Momtahena SJ, Karim R, et al. Trastuzumab-induced toxic epidermal necrolysis in a Her-2-positive metastatic breast cancer patient—A rare case report. *Clin Case Rep*. 2024;12:e9103. doi:10.1002/ccr3.9103