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CASE REPORT

Toxic Epidermal Necrolysis Precipitated by Anti-Malarial Drug Primaquine and Artesunate

Lulwa Alogayell[1], Alanoud A Alsalman[1], Renad AlKanaan[2], Amal H. Abualola[3], Ghaida Almarshoud[1,*] and Ibrahim Alfuraih[1]

[1] Department of Medicine, Division of Dermatology, King Fahad Medical City, Riyadh, Saudi Arabia
[2] College of Medicine, King Saud University, Riyadh, Saudi Arabia
[3] General practitioner, East Jeddah general hospital, Jeddah, Saudi Arabia

Abstract: Toxic Epidermal Necrolysis (TEN) is a life-threatening mucocutaneous reaction that can be triggered by anti-malarial medication. However, TEN precipitated by primaquine and artesunate 2 has been rarely documented in the literature. In this case report, a 47-year-old male, previously diagnosed with malaria, developed TEN following the initiation of anti-malarial therapy with intravenous artesunate and primaquine. The patient presented with a painful, erythematous rash covering 40% of the body surface area, along with oral erosions and ocular involvement. Laboratory findings revealed increased levels of aspartate aminotransferase (AST), thrombocytopenia, and hypoalbuminemia. A skin biopsy confirmed the diagnosis of TEN. The suspected medications were discontinued, and the patient was treated with systemic corticosteroids and a single subcutaneous injection of Etanercept (50 mg). The patient showed significant clinical improvement, with resolution of dysphagia, skin lesions, and no signs of secondary infection. This case highlights the risk of developing TEN following treatment with the anti-malarial drugs primaquine and artesunate.

Keywords: Toxic Epidermal Necrolysis, Anti-malarial drugs, Primaquine, Artesunate, Drug- Induced TEN.

1 Introduction

Toxic epidermal necrolysis (TEN) is a severe, potentially fatal condition characterized by widespread epidermal necrosis. The prevalence of TEN is rare, affecting two to three individuals per million annually in the United States and Europe (1) . It carries a significant mortality risk, reaching up to 40% (1) . The development of TEN has been associated with high drug doses or repeated exposure to certain medications which can result in an exaggerated immune response. Additional risk factors include advanced age, gender, and immunocompromised status (2) . However, reported cases involving primaquine and artesunate are rare.

2 Case Presentation

A 47-year-old male, presented with a painful body rash that started two days prior to his admission, along with fever. The patient reported dysphagia since the onset of rash. The patient's initial symptoms started a month prior to his admission, with intermittent fever, chills, and rigors. His initial diagnosis was malaria, for which he received a course of intravenous artesunate and was discharged on primaquine. Two days after starting primaquine, the patient experienced a diffuse painful body rash. Skin examination revealed erythematosus dusky patches and plaques covering almost 40% of the body surface area, involving the face, trunk, and upper and lower limbs, with a positive Nikolsky sign. Oral erosions were also noted over the hard palate and beneath the tongue, and redness around both eyes (Figure 1).

Laboratory results showed an albumin of 28 g\{}L (low), aspartate aminotransferase (AST) of 104 U/L (high), and neutrophils at 84%. White blood cell (WBC) count was within normal limits, and platelets were at 5710 9 /L (low), and activated partial thromboplastin time (APTT) of 57 4 seconds. The patient was admitted with suspected TEN (SCORTEN:2), likely precipitated by recent treatment

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***Corresponding author:**
✉ Ghaida Almarshoud
Ghaidalmarshoud@gmail.com

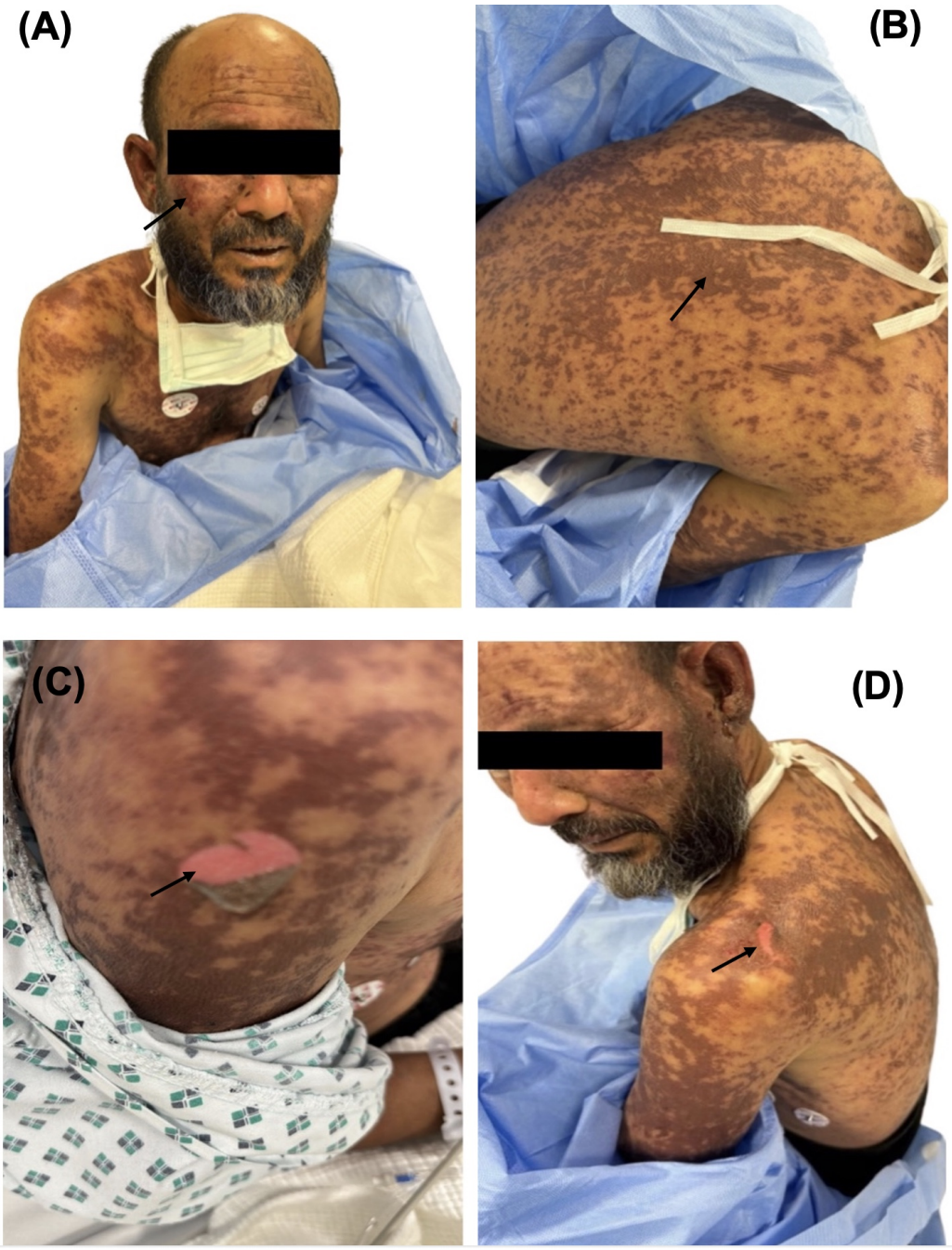

Figure 1. Clinical presentation of Toxic Epidermal Necrolysis (TEN) at admission: (A) Facial involvement with erythematous dusky patches and periorbital erythema. (B) Back view revealing erythematous dusky patches and confluent plaques (C) Close-up view of maximal epidermal detachment demonstrating positive Nikolsky sign. (D) Extensive trunk involvement showing widespread erythematous patches and early epidermal detachment.

with primaquine. Primaquine was discontinued and the patient was started on hydrocortisone 100 mg IV every 6 hours. A single dose of etanercept (50 mg) was also administered. For wound care, the patient was treated with potassium permanganate soak, followed by Fucidin cream for skin erosions, and Vaseline impregnated gauze applied over affected areas. Clobetasol ointment was applied twice daily over dry lesions, particularly over the lower limbs. A skin biopsy helped to confirm the diagnosis of TEN with detached epidermis (Figure 2). Following treatment, the patient was able to resume oral intake without dysphagia, and there was no recurrence of fever. His skin lesions showed signs of healing. Furthermore, there was no evidence of a secondary infection. Albumin levels were monitored, and nutritional support with a high-protein diet was provided. By the time of discharge, the patient's oral lesions had healed, and the skin involvement was significantly improving (Figure 3). All cultures

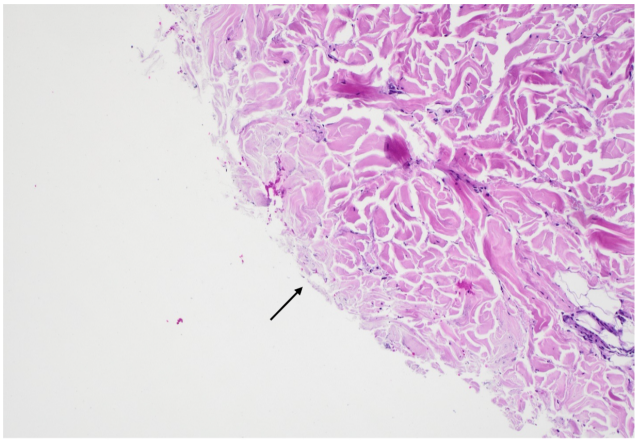

Figure 2. Histopathological findings confirming Toxic Epidermal Necrolysis. Skin biopsy (H&E stain, 40× magnification) showing complete epidermal detachment with full-thickness necrosis. The section demonstrates dermal-epidermal separation with necrotic keratinocytes and minimal dermal inflammation, characteristic of TEN.

returned negative, including the malaria smear, confirming no recurrence of malaria. The patient was discharged with instructions for wound care, including the continued application of Clobetasol ointment, and follow-up appointments.

3 Discussion

This is a case of a 47-year-old male who was diagnosed with TEN after starting treatment with primaquine and artesunate. In the present case, patient developed typical clinical manifestations of TEN which involved erythematous dusky patches and plaques, alongside mucosal involvement and systemic symptoms (3) . Some authors have suggested that the pathophysiology 5 of TEN is quite similar to superficial skin burns (1) . The involvement of ocular epithelium, as seen in the present case, is associated with significant adverse outcomes if not treated during initial stages. Another clinical feature that established the diagnosis of TEN was Nikolsky sign which is a critical indicator of TEN and other skin disorders like pemphigus (4) . Furthermore, laboratory abnormalities in TEN included elevated liver enzymes and activated partial thromboplastin time (APTT) which suggests a disruption in the coagulation pathway. These findings have been reported in severe cases of TEN, often complicating the clinical course (2) . The literature has more commonly implicated drugs like allopurinol, lamotrigine, and antibiotics in TEN (3) . Bashir et al. (2024) demonstrated that various antimalarial drugs like chloroquine and sulphadoxine/pyrimethamine can cause severe skin reactions including pruritus, Steven Johnson syndrome (SJS), and TEN, with significant variability in prevalence and fatality rates (5) . However, Ogiji et al. (2022) showed that artemisinin-based drugs, primarily for malaria treatment, rarely cause severe reactions like SJS or TEN (6) . In this case, the onset of symptoms which were two days after the initiation of primaquine suggests a probable link between the drug and the adverse reaction. This is consistent with the timing of reactions noted in other drug- induced cases of TEN, where symptoms typically begin within the first week of drug therapy. Kommu and Whitfield et al. (2024) illustrated that most cases of TEN occur within the first 1–3 weeks of starting a new drug (7) . The treatment of TEN involves cessation of the suspected causative agent and the initiation of supportive and systemic therapy. Recent studies suggest that etanercept can improve survival rates, providing a rationale for its use in TEN cases (8) . This is a case of a 47-year-old male who was diagnosed with TEN after starting treatment with primaquine and artesunate. In the present case, patient developed typical clinical manifestations of TEN which involved erythematous dusky patches and plaques, alongside mucosal involvement and systemic symptoms (3) . Some authors have suggested that the pathophysiology 5 of TEN is quite similar to superficial skin burns (1) . The involvement of ocular epithelium, as seen in the present case, is associated with significant adverse outcomes if not treated during initial stages. Another clinical feature that established the diagnosis of TEN was Nikolsky sign which is a critical indicator of TEN and other skin disorders like pemphigus (4) . Furthermore, laboratory abnormalities in TEN included elevated liver enzymes and activated partial thromboplastin time (APTT) which suggests a disruption in the coagulation pathway. These findings have been reported in severe cases of TEN, often complicating the clinical course (2) . The literature has more commonly implicated drugs like allopurinol, lamotrigine, and antibiotics in TEN (3) . Bashir et al. (2024) demonstrated that various antimalarial drugs like chloroquine and sulphadoxine/pyrimethamine can cause severe skin reactions including pruritus, Steven Johnson syndrome (SJS), and TEN, with significant variability in prevalence and fatality rates (5) . However, Ogiji et al. (2022) showed that artemisinin-based drugs, primarily for malaria treatment, rarely cause severe reactions like SJS or TEN (6) . In this case, the onset of symptoms which were two days after the initiation of primaquine suggests a probable link between the drug and the adverse

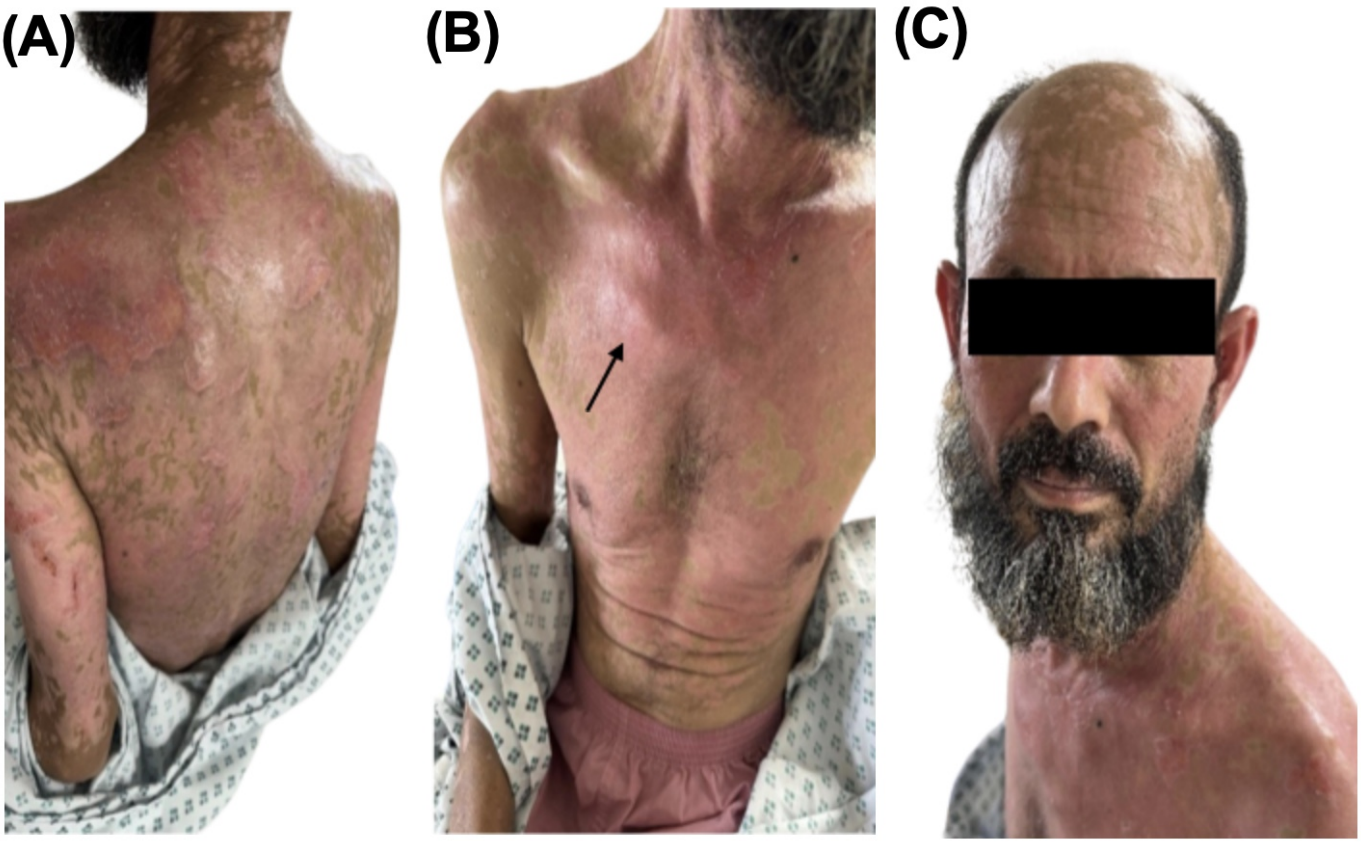

Figure 3. Clinical improvement after 4 weeks of treatment. (A) Back view demonstrating extensive healing and re-epithelialization with minimal post-inflammatory changes. (B) Trunk improvement showing healing with minimal residual erythema and no secondary infection.(C) Facial healing with resolution of erythema and complete re-epithelialization.

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To further find relevant studies like the present case, a review of literature was performed. Only a few studies were identified in literature. A study by Abdallah et al., was conducted over a 10- year period involving 150 patients with SJS or TEN (9) . In 42.7% of cases, TEN was reported whereas in 9.3% cases, TEN and SJS overlap was seen. Their findings showed that artesunate was the most common drug that precipitated the development of TEN, accounting for 20.7% of the cases. Other drugs suspected to induce TEN or SJS were septrin, phenytoin, ciprofloxacin, and carbamazepine (9) . No other study was identified in literature that reported primaquine and artesunate as inducers for TEN. This case adds valuable insight into the spectrum of medications that can potentially trigger TEN and emphasizes the need for heightened awareness among clinicians regarding the early signs of this life-threatening condition. It also reinforces the importance of rapid intervention and a comprehensive therapeutic strategy, which are crucial for improving patient outcomes in TEN.

4 Conclusion

This case adds valuable insight into the spectrum of medications that can potentially trigger TEN, emphasizing the need for heightened awareness among clinicians regarding the early signs of this life-threatening condition. It also reinforces the importance of rapid intervention and a comprehensive therapeutic strategy, which are crucial for improving patient outcomes in TEN. The findings from this case should encourage further investigation into both the mechanisms and management of drug-induced TEN, enhancing the healthcare provider's ability to predict

and mitigate this severe adverse reaction effectively.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethical Statement

Written informed consent was obtained from the patient to be included in this study. Institutional review board (IRB) approval from King Fahad Medical City (KFMC) was also obtained

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Citation

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