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Toxic epidermal necrolysis induced by COVID-19

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Abstract

Toxic epidermal necrolysis (TEN) is a life-threatening acute mucocutaneous syndrome. It is characterized by keratinocyte necrosis and apoptosis, which affect more than 30% of the body's surface. TEN is most commonly due to an altered immunological response to specific drugs, infections, and malignancies, or it can be idiopathic. The combination of TEN and COVID-19 can have a fatal outcome if not recognized and promptly treated. Therefore, fast reporting of such cases will draw doctors' attention to quick and right intervention. In this article, we present a 66-year-old patient with a clinical presentation of toxic epidermal necrolysis along with a coexisting COVID-19 infection. To our knowledge, this is the first case of TEN in a patient diagnosed with SARS CoV-2 infection in Saudi Arabia.

Introduction

Toxic epidermal necrolysis (TEN) is a life-threatening acute mucocutaneous syndrome. TEN is characterized by keratinocyte necrosis and apoptosis affecting more than 30% of the body's surface [1]. It is a rare disease; the annual incidence of SJS and TEN in the general population is known to be 1–6 and 0.4–1.2 per million people, respectively. A study conducted in the Qassim region, Saudi Arabia, estimated the incidence rate of SJS/TEN to be 7.6 cases per million person-years [2,3]. Mortality reaches up to 40% [1]. Patients with TEN syndromes present with systemic symptoms along with skin tenderness, erythema, hemorrhagic desquamation, and epidermal separation, which can be described as patches and blisters of eroded skin. These symptoms frequently begin on the face and parasternal region before spreading to the entire body [4]. However, in virtually all instances, the scalp is usually unaffected. Also, one of the important signs in physical examination that supports the diagnosis of TEN is the Nikolsky sign, which occurs when a small force is applied to the skin, causing the epidermal layer to separate from the underlying surface [4].

Toxic epidermal syndrome usually develops over 2 weeks after the insult. However, it can suddenly progress to attack the entire body in a matter of 24 hours [4]. Furthermore, TEN most commonly occurs due to an immunological response to specific drugs. Infections, tumors, and vaccines can also induce TEN, but rarely [5]. One example of a recent infection that is suspected to cause TEN is COVID-19, which is a severe acute respiratory syndrome with a variety of clinical symptoms. Furthermore, COVID-19 induces an inflammatory reaction that lowers the threshold of drug reactions and may predispose COVID-19 patients to TEN [6]. Here, we present a case of biopsy-proven TEN in a patient who had a current COVID-19 infection.

We present the following case in accordance with the CARE reporting checklist.

Case report

A 66-year-old Saudi male patient was presented to the ER on June 21, 2022, by ambulance with generalized, scaly, erythematous, crusted, peeling, and blistering skin lesions over more than 50% of the body area (upper and lower extremities, trunk, back, face and groin areas). (Figure 1). The rash was preceded by a fever and started on the third day. The patient presented with instability of vital signs: Temperature: 39 Celsius; respiratory rate: 35; blood pressure: 140/75; heart rate: 69; oxygen saturation: 99. He also had an altered mental status. The patient had received two doses of the COVID-19 vaccine, and the last dose was administered 10 months before the onset of the insult. Moreover, there was no family history of a similar condition. Additionally, the patient had had no known contact with any ill persons or persons infected with COVID-19. However, when the patient was admitted to the intensive care unit, a nasal swab was taken and gave a positive result.

On physical examination, the patient was unconscious with a Glasgow Coma Scale of 4 out of 15 under the effect of sedation. Beside the cutaneous manifestations mentioned in the history, the skin showed generalized confluent areas of erythema with dusky centers and flaccid blisters. There was oral hemorrhagic ulceration, as well as ocular and genital maceration. An ophthalmologicalexamination was unable to be performed, due to severe eyelidadhesion and symblepharon formation, which are separated under local anesthesia with the blunt tip of a glass rod. After that, a full ophthalmological exam was done.

The anterior segment of both eyes showed conjunctival injection with chemosis, and palpebral edema with crusts, mucopurulent discharge, and eyelid skin sloughing. The corneal and rest of the anterior segment exams were normal. The posterior segment exam was not visualized.

The Nikolsky sign was positive. In addition, the patient's Score of Toxic Epidermal Necrolysis (SCORTEN) was 3. Investigations were conducted and recorded (Table 1). Beside the positive PCR test, a chest X-ray was taken and revealed bilateral opacities in the lower zones along with pleural effusion, which supports the diagnosis of COVID-19 pneumonia (Figure 2). Moreover, the septic workup showed gram-positive cocci in clusters (coagulase-negative *Staphylococcus Acinelobacier calcoaceticus-baumannii* complex) and gram-positive bacilli (*Corynebacterium* sp.) in the blood. Also, there were gram-negative bacilli (*Pseudomonas aeruginosa* and *Klebsiella pneumoniae*) on the skin. The skin biopsy was performed, and the haematoxylin and eosin stains showed full thickness epidermal necrosis with re-epithelization. The superficial dermis shows a mixed inflammatory infiltrate (Figure 3). Direct immunofluorescence from the perilesional skin was negative. A clinical diagnosis of toxic epidermal necrolysis (TEN) confirmed by the dermatologist was formulated. The patient was resuscitated and was given proper ICU and medical care, including

starting him on hydrocortisone 200 mg, which was then reduced gradually by 20 mg every 3 days until the patient was completely weaned off the medication.

Several laboratory investigations were done to exclude possible confounding factors that may induce the incidence of toxic epidermal necrolysis. The following list of laboratory tests results were all negative:

- (HBS AB, HBSAG, HAV Abs, HCV AB CMV PCR, Varicella Zoster virus IGG, ANCA PROFILE ANTI-NDNA IFA, Rheumatoid Factor, Anti JO-1 HISTDYL-TRNA SYNTHETASE, B-HCG).
- Tumor Marker: (CA 125, CA 15-3, CA 19, ALPHA fetoprotein).

The patient received a treatment plan consisting of intravenous immunoglobulin (IVIG) at a dosage of 400 mg/kg/day for 5 consecutive days, along with topical steroids and white paraffin, to address their skin condition. An urgent ophthalmology referral was made due to ocular maceration, and for eye treatment, the patient was prescribed an ointment containing a combination of dexamethasone and neomycin sulfate, to be applied twice a day, as well as tobradex drops to be used every 2 hours with heavy lubrication.

Additionally, the patient was put on antibiotics, specifically vancomycin at a dosage of 500mg and Linezolid at a dosage of 2mg. The patient's skin condition showed a significant improvement after the first day of IVIG treatment, and the progress of the skin condition was monitored over a period of 5 weeks until it was completely resolved. (Figure 4).

Discussion

The case of a patient with TEN and a history of a recent COVID-19 infection was presented in this report. Drug use is the main cause of TEN/SJS. It typically manifests 4 to 28 days following drug exposure, highlighting the significance of getting a complete history of drug use [7]. Viruses (Coxsackie, influenza, Epstein-Barr, human herpesvirus 6 and 7, cytomegalovirus, parvovirus), bacteria (*Streptococcus* group A), mycoplasma pneumonia, and mycobacterium infections have all been linked to cases [7]. It is thought that COVID-19 infection can enhance specific immune system responses, or cytokines, which may raise a person's risk of experiencing life-threatening allergic reactions like TEN/SJS. This has been seen in other immune system-deficient illnesses, such as HIV, and some specialists hypothesize that post COVID-19 TEN/SJS may be an entirely new form of immune response known as immunological reconstitution inflammatory syndrome (IRIS) [11].

There have been six reports of TEN/SJS cases linked to COVID-19 infections, including two cases in the UK [5,8] and a single case in each of the following countries: Qatar [7], Italy [9], Iran [6], and India [10]. Interestingly, our case was the first case in Saudi Arabia, specifically in Medina. Skin

lesions were identified in 0.25 percent of cases among more than 5,000 pediatric patients with COVID-19 infection. Only one patient, who also had lung involvement from SJS/TEN, died unexpectedly [7]. Another reported case of a COVID-19-infected 8-year-old child who also experienced lung involvement and a SJS/TEN rash has been documented. With the help of IVIG, steroids, and cyclophosphamide, the child's condition improved [7]. In our case report, the relationship between COVID-19 infection and TEN syndrome may be clear, as the patient did not have a history of any medication use before the insult. This means that the COVID-19 infection could be one of the possible triggers. The whole history and clinical examination of our patient gomore towards COVID-19-induced TEN.

This study faced many limitations that led to some difficulties in gathering important information that may be helpful to reach and confirm the diagnosis. One of them is that the patient was comatose, so if he was alert and cooperative, he would have helped us at least with some of the helpful personal histories. The other thing is that we didn't have access to the patient all the time because of the patient's condition, so it took us a lot of time to get enough information.

Conclusions

Although TEN is a rare condition, it is a serious dermatological emergency. It should be treated right away to decrease mortality. Thus, the purpose of this case report was to raise awareness of the possibility of significant COVID-19-induced TEN and can serve as a valuable example to inform other providers of an effective treatment strategy for a previously unknown sequela of COVID-19 infection.

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Figure 1. Clinical presentation of the dermatological lesions at hospital admission. The images demonstrate generalized, scaly, erythematous, crusted, peeling, and blistering skin lesions over more than 70% of the body area (upper and lower extremities, trunk, back, face, groin, and pubic areas) with oral hemorrhagic ulceration as well as ocular and genital maceration.

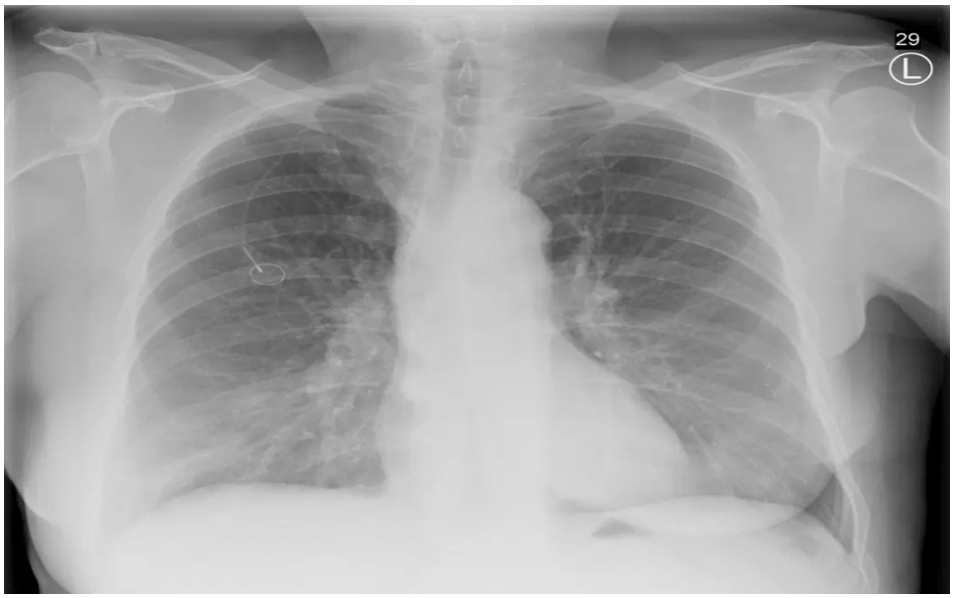

Figure 2. Radiological findings showed opacification in the lower zone of bilateral lung fields, partial obscuration of bilateral costophrenic angles, and bilateral opacities in the lower zones, along with pleural effusion.

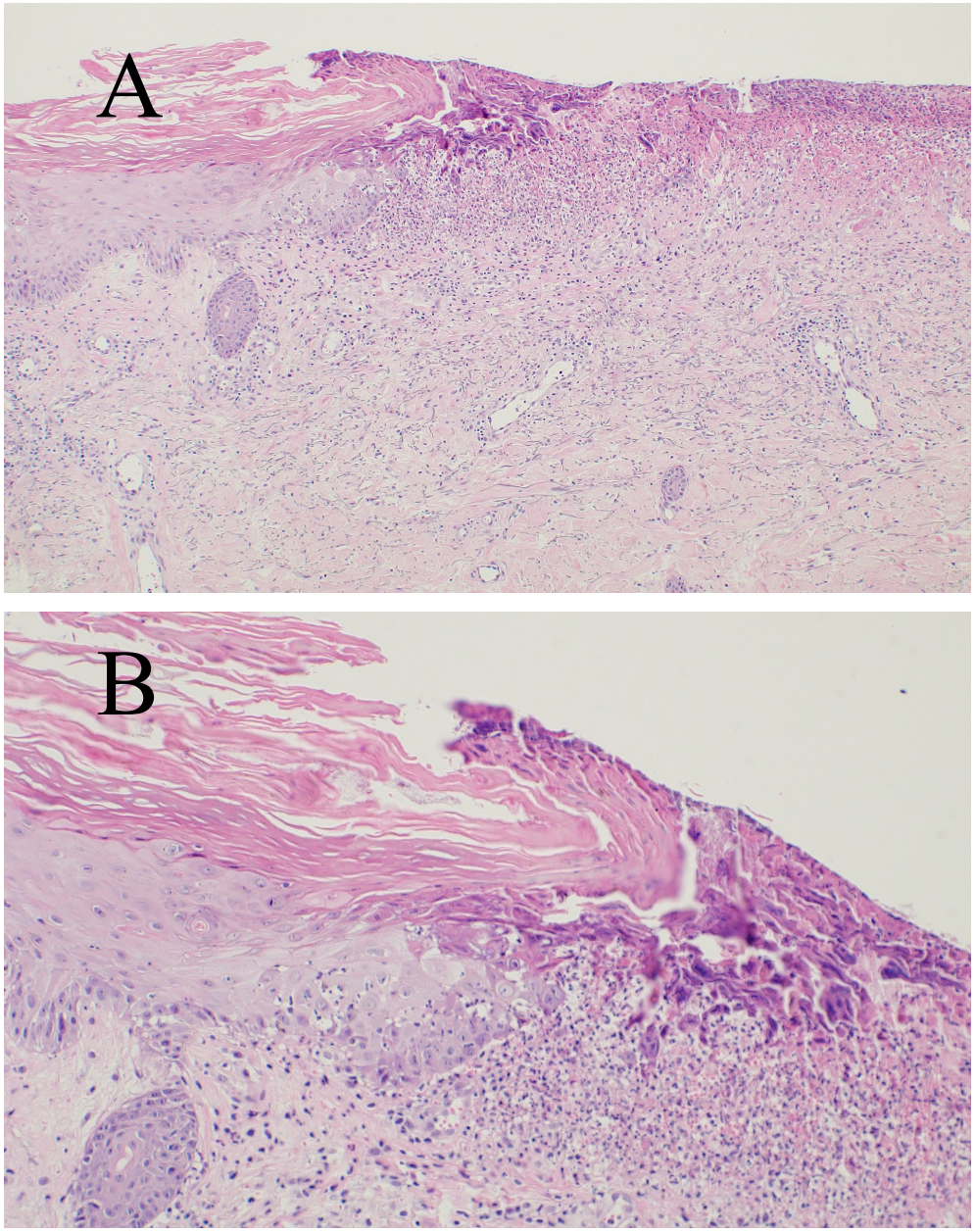

Figure 3. Full thickness epidermal necrosis, see necrotic keratinocytes at the edge. The epidermis demonstrates necrosis, degeneration, dyskeratotic keratinocytes, and necrotic keratinocytes. There is a severe dermal inflammatory infiltrate (lymphocyte and histocytes) but no neutrophils. No leukocytoclasis, no microabscesses.

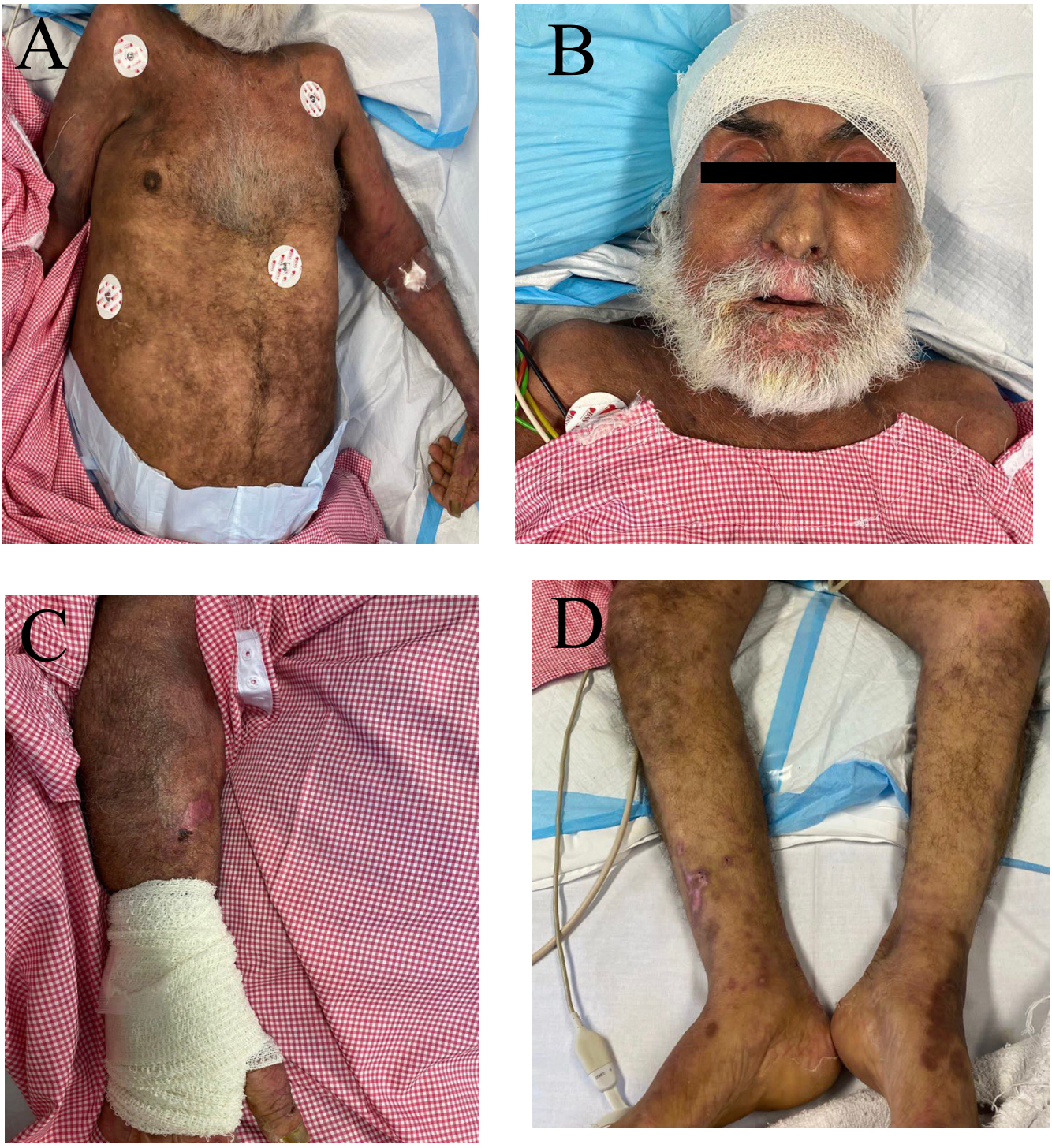

Figure 4. Clinical presentation of the dermatological lesions after one month of treatment.

Parameters	Results	Normal Range
White blood cell	6.31 K/µL	4 – 10
Red blood cell	3.42	4.5 – 5.5
Hemoglobin	9.2 g/dl	13 – 17
Hematocrit	30.3%	40 – 50
Platelet	155	150 – 410
Neutrophil	5.567	2 - 7
Lymphocyte	0.07	1- 3
AST	10U/L	10 - 50
ALT	10U/L	40 – 129
ALP	79U/L	44 - 147
GGT	23U/L	5 - 40
Bilirubin total	15 µmmol/L	0 – 18
Albumin	18	30 – 50
Creatinine	57 mmol/L	44 - 115
Urea	5.5 mmol/L	2.5 – 8.3
PT	15.3	11 - 16
PTT	29.6	26 - 36
INR	1.25	0.9 - 1.4
Sodium	146 mmol/L	136 - 145
Potassium	3.5 mmol/L	3.5 – 5.1
Calcium	1.82 mmol/L	2.06 – 2.5
T 4	6.95 pro/L	7.9 – 18
Free T3	1.53 pro/L	3.39 – 6.85
TSH	2.8 mlU/1	0.34 – 5.6
COVID- 19 PCR	Positive	Negative

Table 1. Patient investigations.

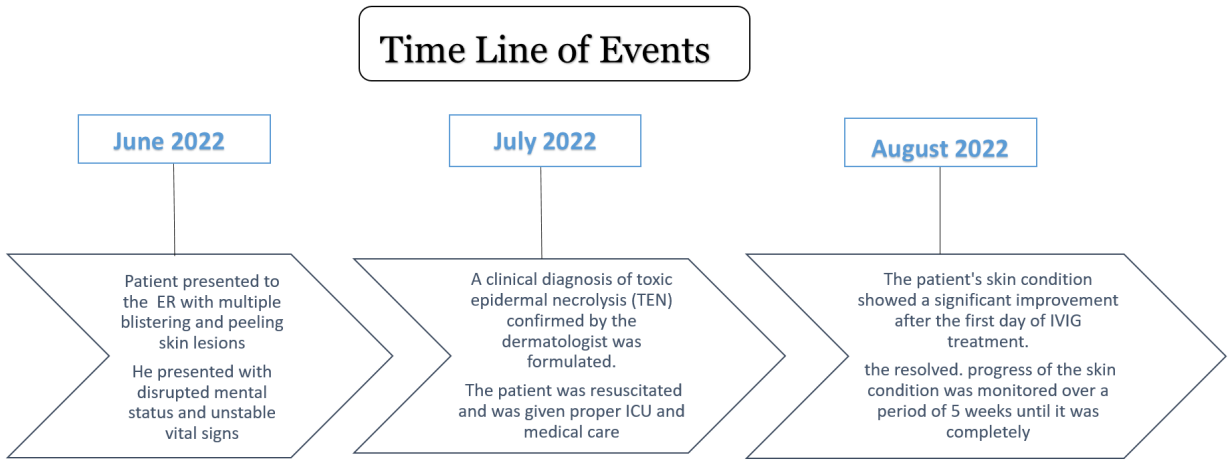

Figure 5: Timeline displays the chronological order of the patient's condition.