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Nevirapine Induced Toxic Epidermal Necrolysis Managed Successfully with Etanercept (A Case Report)

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Abstract Toxic epidermal necrolysis (TEN) is a rare, idiosyncratic, unpredictable drug reaction. It is potentially a life threatening dermatological disorder. At present there is no definite consensus regarding the management of TEN. Treatment of TEN with etanercept has shown promising results in the recent literature where conventional systemic therapies are either contraindicated or have failed. We report a case of nevirapine induced TEN treated successfully by administering single dose of 50 mg etanercept given subcutaneously that resulted in complete re-epithelialization and without any complications.

Keywords: *adverse drug reactions, reverse transcriptase inhibitor, SCORTEN, Etanercept, Naranjo's ADR probability scale*

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1. Introduction

Toxic epidermal necrolysis (TEN) is a rare, idiosyncratic, unpredictable drug reaction having high incidence mortality. The western literature reported incidence of TEN between 0.5 to 1.89 cases/million/year. [1] Its pathogenesis is unclear and classification is delineated by the presence of mucosal involvement and percentage of body surface area involved i.e., epidermal detachment of over 30% of total body surface area. [2] Various etiological factors have been proposed regarding TEN but the most common incriminating agents are drugs e.g., sulfonamides, carbamazepine, antibiotic (aminopenicillins), anticonvulsants, Non-steroidal anti-inflammatory drugs (NSAIDS), allopurinol, chlormezanone, lamotrigine, nevirapine etc. [3] There is paucity of therapeutic guidelines regarding its management and various treatment modalities have been suggested e.g., corticosteroids, thalidomide, pentoxifylline, plasmaphereis, cyclophosphamide, GCS-F, TNF-α to cyclosporine.[4] This case report highlights the importance of etanercept in managing a case of nevirapine induced TEN.

2. The Case

A 19-year old nursing student presented to emergency department of Command Hospital, Chandimandir (Haryana) India after receiving an accidental needle prick injury while drawing a blood sample from an indeterminate HIV-seroreactive patient admitted in the Acute Medical Ward. She was started on ART in the form of triple combination as per WHO guidelines (zidovudine, lamivudine and nevirapine) for three days as part of post-exposure prophylaxis, while awaiting confirmatory results. On fourth day of therapy, she developed an itchy, maculo-papular rash on face, arms and upper trunk along with fever. Fever was continuous, moderate in intensity being unresponsive to antipyretics. These skin lesions continued to progress and in the next two days, becoming bullous, confluent, purpuric lesions with separation of epidermis over the back, buttocks, limbs and chest involving 80% of total body surface area (TBSA). [Figure 1-Figure 3] On general physical examination, she was toxic and ill looking though her vitals stable with persistent tachycardia ranging from 110-140 beats/minute. Severe oral involvements were also present in the form of painful haemorraghic erosions over the lips, buccal and pharyngeal mucosa restricting her oral intake. Genital examination showed multiple erosions over the inner surface of anal and vaginal mucosa. Ophthalmic involvement showed watering and photophobia along with conjunctival redness. Skin was tender and Nikolsky sign positive. There was no past history of tuberculosis, jaundice, bronchial allergy, diarrohea or upper respiratory tract infection. Her family history for demyelinating disease was negative.

3. Laboratory Work up was as under

Her initial biochemical, hematology and coagulation profile, X-ray chest, antinuclear antibodies (ANA),

procalcitonin levels were within normal limits. Serological examinations of HCV, HBV, Herpes and HIV were negative. Tzanck smear, grams staining, urine, fungal, wound and blood cultures were all negative.

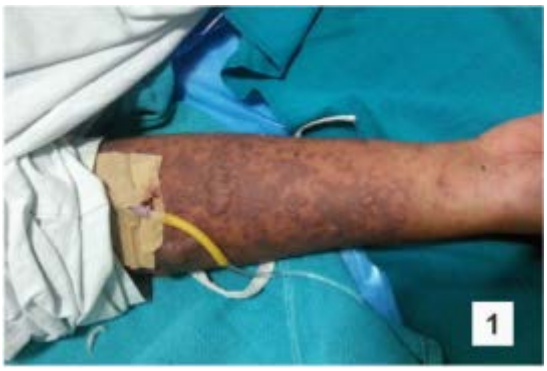

Figure 1. Patient at the time of emergency showing atypical purpuric and bullous target lesions over the forearms

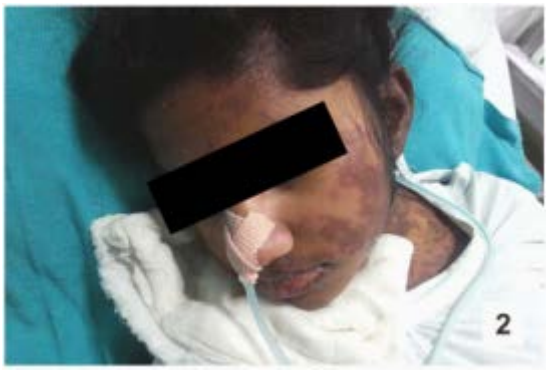

Figure 2. There was haemorraghic crusting of the lips and mucopurulent discharge from her eyes

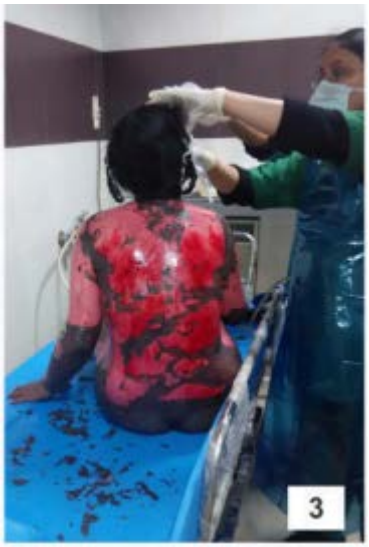

Figure 3. Epidermal separation seen over the back on day four

A diagnosis of Toxic epidermal necrolysis due to nevirapine was made clinically on the basis of drug ingestion (nevirapine), clinical features supported by laboratory findings. Antiretroviral therapy (ART) was stopped and the case was managed with multidisciplinary approach. Fluids requirements were calculated and crystalloids were started. She was started on cyclosporine at a dose of 4mg/kg, (12 hourly for 9 days).Third generation cephalosporin and aminoglycoside (Ceftriaxone and Amikacin) were added to prevent any super added infection. Vaseline impregnated gauze was used for lips along with oral aesthetic gel to reduce the oral pain. Ophthalmic treatment included a combination of antibiotic and steroid preparation. Vaseline dressing in the genital area was also used to prevent synechiae formation. Injection morphine was used as and when required for reducing pain along with barrier nursing care, nasogastric feeds, catheterization, sofratulle dressing for erosions. High protein diet was given. Debridement of necrotic skin was done followed by nanocrystalline silver as closed dressing. Her SCORTEN score on day fourth was 4 with expected mortality of 58.3% and Naranjo's ADR probability scale score of 8 indicating probable adverse drug reaction. Her higher mental function and other systemic examinations were normal but fever persisted and skin lesions continued to progress.

On 7th day of her admission, active oozing from the lesions increased greatly and copious ooze prevented open dressing from staying in place and her general condition deteriorated. She passed frank melena on day 8th and 9th. On 10th day, she had continuous, high grade fever ranged between 104-105 F and pulse rate from 140 to 170 beats per minute while skin erosions and mucosal ulcerations continued to progress unabated. Her hemoglobin levels decreased to 8.2 g/dl, SGOT and SGPT increased to 236 and 254 IU/L respectively. The plasma protein levels decreased significantly (Albumin 2.2 g/dl, globulin 1.8g/dl, total 4.0 g/dl).

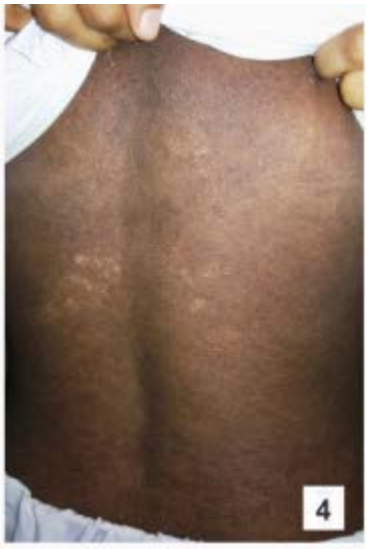

Figure 4. Patient showing complete re-reepithelialization along with hyperpigmentation during her recovery phase

In view of the young girl's rapid downhill course, Medical College consultation was taken and after reaching consensus amongst the treating physicians, the patient was given injection etanercept 50 mg subcutaneously on tenth day and cyclosporine was discontinued. The dressings were changed periodically and antibiotics were continued. Two units of packed RBCs were transfused on day 11th and four units of Fresh Frozen Plasma on day 12th. There was a remarkable improvement in general condition of the patient within 48 hours of etanercept administration. Patient became afebrile by 15th day and her antibiotics were stopped. Re-epithelialisation started and progressed gradually, her oral ulcers healed sufficiently by the 18th

day, allowing her to take oral feeds. Ryle's tube and catheter was removed on the same day. The skin lesions healed completely within the next ten days (i.e., on 28th day of her admission) with patchy hyper-pigmentation without scarring of the skin or mucosa. [Figure 3-Figure 5] She was discharged from the hospital on 28th day. Oral re-challenge test with nevirapine was not done on ethical grounds because of higher risk of mortality and on good clinical practice guidelines of Helsinki's i.e., do-no-harm. During the post treatment follow-up period of six months following discontinuation of nevirapine and etanercept, the patient reported complete resolution of her symptoms without any sequel.

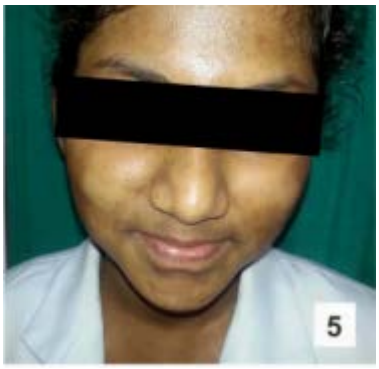

Figure 5. Patient showing complete re-reepithelialization along with hyperpigmentation during her recovery phase

4. Discussion

Diagnosis of TEN mainly relies on clinico-pathological features and its treatment consists of prompt diagnosis, discontinuation of suspected drug, appropriate symptomatic medication, fluid replacement and meticulous wound care. At present there is no uniform strategy for managing TEN. [5] Role of systemic steroids in the management of TEN has been always associated with controversies and they even demonstrated to have worsened the outcome. [6] Similarly, EuroSCAR study based on the retrospective analysis of 289 patients found no benefit from corticosteroids or immunoglobulins (IVIG) compared to supportive care alone. [7] Even, the combination therapy of steroids and IVIG did not find its merits in decreasing the mortality rates. [8] However, several case reports and case series revealed encouraging results with the use of cyclosporine (CsA) in stopping disease progression and to prevent the mortality [9,10] prompting us to use CsA as first line therapy in our patient. Further, CsA is useful in the treatment of TEN as a rapid and potent inhibitor of IL-2 that is associated with rapid healing and improved survival by targeting T lymphocyte functions through IL-2, inhibition of macrophage activity [11] and inhibition of the activation of the Fas receptor (CD95R)-Fas ligand system (CD95L) thereby blocking drug induced keratinocytes apoptosis. [12] An additional mechanism of immunosuppressive is the inhibition of CD8 T cell activation, which in turn inhibits apoptosis and destruction through Fas ligand or perforin / granzyme pathway [11] making CsA an excellent choice for the treatment of TEN.

Tumor necrosis factor alpha (TNF-α) plays an important role as a molecular bridge in keratinocytes apoptosis in TEN. [12] Etanercept, an anti TNF-α biologic has been used with promising results in a series of cases of TEN. [13] Rationale for therapeutic intervention with etanercept is that the TNF-α inhibitor may be an effective agent to decrease epidermal apoptosis among patients with TEN as increased amounts of TNF-α are observed in the epidermal lesions of TEN. Paul et al [14] elucidated that TNF-α released by cytotoxic T lymphocytes could induce epidermal apoptosis by binding to TNF-α receptors on the surface of keratinocytes in TEN. Etanercept a recombinant fusion protein consisting of extracellular portions of human TNF-α p75 moieties fused to the Fc domain of human IgG1 acts by neutralizing s TNF, blocks it's binding to the receptor, interrupting the subsequent signaling and inflammatory pathways. [15] Anti- TNF-α therapy therefore, down-regulates the monocytes capacity to produce pro-inflammatory cytokines and induces a shift to produce more inflammatory TH2 cytokine. [16] According to the protocols published by the University of Miami in 2007, including guidelines for TEN therapy, nonadhesive dressings with 0.05% silver nitrate changed every three days are sufficient for infection control. [17]

In the present case, the patient was prescribed nevirapine as a part of post exposure prophylaxis (PEP). Nevirapine is associated with a high risk of idiosyncratic severe cutaneous reactions due to its long elimination half life (25-30h). The diagnosis in this case was based on history, clinical and laboratory findings as patient denied consent for histopathological examination. SCORTEN [18] and Naranjo's adverse drug reaction probability scale [19] were used to access the mortality and the causal relationship between the drug and development of adverse reaction. Etanercept had been administrated as a single dose of 50mg subcutaneously [20]. Addition of nanocrystalline silver dressing resulted in enhanced healing and better survival. Cyclosporine failure was suspected as it was given in a dose of 4mg/kg/day for nine days while the patient condition deteriorated suggesting that other mechanisms are involved in the pathogenesis of TEN i.e. TNF-α.

This case report highlights the importance of etanercept in the management of nevirapine induced TEN after cyclosporine failed to halt the progression of the TEN. It lends support to this view that etanercept is safe and effective in the management of TEN, even when administered later in the course of the disease progression i.e. on 10^{th} day while earlier case series and studies have advocated its use within 6 hours to 96 hours in the management of TEN. Further, studies are required to substantiate these intriguing findings.

What is new?

- Etanercept is a novel treatment modality for managing nevirapine induced TEN.
- Etanercept was administered later in the course of the disease progression i.e. on 10^{th} day while earlier case series and studies have advocated its use within 6 hours to 96 hours in the management of TEN.
- Etanercept was used after cyclosporine failed to halt the progression of the TEN.

Acknowledgement

Nil.

Conflict of Interest

None declared.

Patients Consent

Written informed consent was obtained from the patient for publication of this case report.

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