Journal of Rawalpindi Medical College (JRMC); 2017;21(2): 187-188

Case Report

Toxic Epidermal Necrolysis

Syed Naveed Ali Shah, Ifaza Tariq, Muhammad Nauman Zafar
Department of Medicine, Benazir Bhutto Hospital, Rawalpindi.

Toxic epidermal necrolysis (TEN) is the most severe form of drug-induced skin reaction and includes denudation of >30% of total body surface area. The mechanism of disease is not completely understood, but immunologic mechanisms, cytotoxic reactions, and delayed hypersensitivity seem to be involved. Drug-induced toxic epidermal necrolysis (TENS), also known as Lyell's syndrome, remains one of the most dramatic dermatological emergencies characterized by extensive destruction of epidermis and mucosal epithelia that often can be caused by drugs. TEN affects between 0.4 and 1.5 cases per million people every year with a mortality rate between 15% to 40%, with a large portion of patients dying from infections or multi-organ failure.[1-4] The pathogenesis of drug-induced TEN is unknown, although several theories have been developed. Recent discoveries have shown that keratinocytes in TEN undergo apoptosis, not simply necrosis.[5,6] Further research has elucidated that this apoptosis can be induced by interactions between cell surface death receptor Fas and its ligand, FasL or CD95L. The management of these patients is primarily supportive, although the use of corticosteroids and intravenous immunoglobulin (IVIG) therapy has been widely used with controversy. We report a case of risperidone induced toxic epidermal necrolysis with excellent response to corticosteroid.

Case report

A 45 yrs old woman with a long history of depressive illness was hospitalized in Benazir Bhutto Hospital, Rawalpindi for an acute episode of generalized body blisters formation. She reported no previous history of allergy to any medication upon admission. The patient developed hypovolemic shock requiring aggressive fluid resuscitation; CVP was 2cm of H2O. Laboratory findings revealed moderate hyperglycemia and raised CRP (70 mg/dl). The rest of the investigations were within normal limits. The patient started taking Risperidone one week back. On the third day, an erythematous rash and flaccid blisters appeared on her back and arm. The intake of medication was stopped immediately. The cutaneous rash progressed onto the trunk, face, and limbs reaching almost 52% of the body surface, blisters appeared progressively on the erythematous areas during the following 2 days. There was >30% skin epidermal detachment. A calculated SCORTEN value of 3 predicted a 35.8% mortality rate. Bilateral conjunctivitis and erosions of genital and oral mucosa also developed. The diagnosis of TEN was based on typical history and clinical findings of patient. Skin biopsy was planned but was delayed to avoid the risk of infections. The patient was placed on a fluidized bed and benefited from supportive and antiseptic measures. Systemic corticosteroids were given. Massive rehydration was undertaken with strict vital monitoring. Over the next 48 hours, there was involvement of >90% body surface area. The Nikolsky sign was positive. There was an erosive lesion of skin and mucosa involving eyes (Figures 1 & 2). She was discharged after 15 days with complete epithelialization.

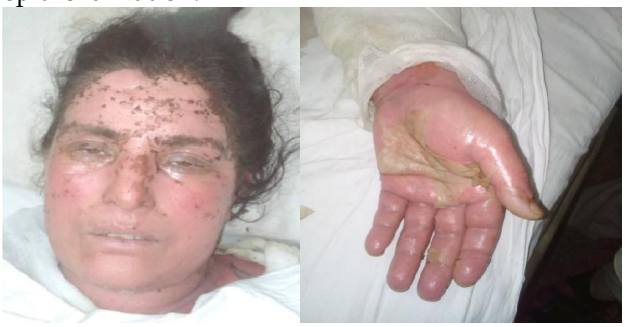

Figure 1&2: Toxic Epidermal Necrolysis

Discussion

The Stevens-Johnson syndrome and TEN represent the different degrees of acute mucocutaneous reaction that often can be caused by drugs.[1] TEN is most commonly characterized by skin changes (scattered 2-ring target-like lesion with a dark red center and a lighter red halo and macules with central blistering that can coalesce to larger areas of denuded skin), hemorrhagic mucositis (mouth, eyes, genitals, and respiratory tract), and systemic symptoms (fever, malaise, and possible internal organ involvement).[3] SCORTEN, a TEN specific severity of illness scale, has been proven to be an accurate predictor of mortality in patients with TEN by evaluating 7 independent risk factors(age, presence of malignancy, body surface area involved, serum blood urea nitrogen level, glucose level, bicarbonate level, and heart rate).[7]

Recent discoveries in the immunopathogenesis of TEN have shown that keratinocytes undergo apoptosis, not

simply necrosis, following different phases.[10,11] Phase 1 is determined by the immunogenic impact of xenobiotics. It involves a lack of balance between the activation and detoxification process in keratinocytes. Phase 2 corresponds to the early apoptosis. The generation of strongly electrophilic metabolites in TEN keratinocytes is thought to lead to disruption of the electron transfer chain in mitochondria. In a TEN keratinocyte it is likely that reactive oxygen species (ROS), acting as messengers, increase gene transcription of the TNF-a and CD95 proapoptotic systems.[11]In late apoptosis (Phase 3) the proinflammatory cytokine TNF-a is believed to act as an autocrine/paracrine factor on neighbouring keratinocytes, thus spreading epidermal destruction. In phase 4 cells with ruptured mitochondria are at risk of death through a nonapoptotic mechanism resembling necrosis.[12] There is currently no specific treatment for TEN. Discontinuation of suspected drugs with supportive care (e.g. wound care, hydration, and nutritional support) forms the basis of treatment.[4] Intravenous immunoglobulin therapy (IVIG) is considered by many clinicians as a treatment option, blocking the blinding of CD95L.[13] An updated review stratified results according to TEN and SJS, and 14 studies in patients with TEN are evaluated. The majority of studies reported positive results, while three cohort studies did not observe statistically significant improvement with IVIG administration. [14] In a sub-analysis of these controlled trials, mortality rates of patients receiving IVIG was 27% compared with 30% of predicted/ control group. Because of the heterogeneity of studies, a meta-analysis could not be conducted for IVIG in TEN or SJS.

N-acetylcysteine (NAC) is a cysteine derivative precursor of GSH. Abnormal inherited metabolic pathways are presumed in some cases, which could lead to diminished detoxifying capacity. Administration of N-acetylcysteine enhances the oxidant buffering capacity of glutathione and inhibits nuclear factors kappa B, a transcription factor induced by TNF-a and interleukin-6. Few patients have been successfully treated with high dose intravenous NAC in open-label studies.[15,16] Further studies are required to confirm the beneficial therapeutic effect of NAC in TEN. In our patient, a good response was achieved with corticosteroids with supportive care showing the potential beneficial effect in TEN. Different studies had used thalidomide, cyclosporine, infliximab, azathioprine, methotrexate, cyclophosphamide, and plasmapheresis but were limited data to be recommended as first-line treatment.[17,18] It is important to identify patients at a risk to avoid delaying therapy. It is suggested that several molecular targets that block different apoptosis/necrosis pathways should be attacked simultaneously to achieve optimal efficacy in the treatment of TEN.

References

1. .J. Revuz, Alan Lyell and Lyell's syndrome. Journal of the European Academy of Dermatology and Venereology 2008; 22(8):1001–02.
2. Schöpf A, Stuhmer B. Rzany N, Victor R.Toxic epidermal necrolysis and Stevens-Johnson syndrome: an epidemiologic study from West Germany. Archives of Dermatology 1991;127(6):839–42
3. Revuz D, Penso J, Roujeau C.Toxic epidermal necrolysis: clinical findings and prognosis factors in 87 patients. Archives of Dermatology 1987; 123(9): 1160–65
4. Garcia-Doval L. LeCleach H, Bocquet X L, Otero J.Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death?. Archives of Dermatology 2000;136(3):323–27.
5. 5.C. Paul P, Wolkenstein H, Adle L.Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis. British Journal of Dermatology 1996;134(4):710–14
6. 6 Viard P, Wehrli R, Bullani M. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. Science 1998; 282(5388): 490–93.
7. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC. Scorten: a severity-of-illness score for toxic epidermal necrolysis.Journal of Investigative Dermatology 2000; 115(2):149–53.
8. Ducic I, Shalom A, Rising W, Nagamoto K, Munster AM. Outcome of patients with toxic epidermal necrolysis syndrome revisited. Plastic and Reconstructive Surgery 2002;110(3): 768–73.
9. Mockenhaupt M, Viboud C, Dunant A.Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. Journal of Investigative Dermatology 2008;128 (1):35–44.
10. 10.Paul C, Wolkenstein P, Adle H.Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis. British Journal of Dermatology 1996; 134 (4): 710–14.
11. 11 Viard I, Wehrli P, Bullani R.Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. Science 1998; 282,(5388):490–93.
12. Green DR and Reed JC.Mitochondria and apoptosis. Science 1998;281(5381):1309–12.
13. Ito K, Hara H, Okada T, Shimojima H.Toxic epidermal necrolysis treated with low-dose intravenous immunoglobulin: immunohistochemical study of Fas and Fas-ligand expression. Clinical and Experimental Dermatology 2004; 29(6): 679–80.
14. Mittmann N, Chan B, Knowles S, Cosentino L.Intravenous immunoglobulin use in patients with toxic epidermal necrolysis and Stevens-Johnson syndrome. American Journal of Clinical Dermatology 2006; 7(6):359–68.
15. Velez A and Moreno JC.Toxic epidermai necrolysis treated with N-acctylcysteine.Journal of the American Academy of Dermatology 2002; 46: 469–70.
16. Redondo P, De Felipe I, Pena DL, Aramendia JM.Drug-induced hypersensitivity syndrome and toxic epidermal necrolysis. Treatment with N-acetylcysteine. British Journal of Dermatology 1997;136(4): 645–46.
17. Gerull R, Nelle M, Schaible T.Toxic epidermal necrolysis and Stevens-Johnson syndrome: a review. Critical Care Medicine 2011; 39:1521–32.
18. Harr T and French LE.Toxic epidermal necrolysis and Stevens-Johnson syndrome.Orphanet Journal of Rare Diseases 2010; 5:39–50.

.