

## Toxic Epidermal Necrolysis

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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 multiorgan failure.<sup>1-4</sup> 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.<sup>5,6</sup> 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 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. Patient developed hypovolemic shock requiring aggressive fluid resuscitation, CVP was 2cm of H<sub>2</sub>O. Laboratory findings revealed moderate hyperglycemia and raised CRP (70 mg/dl). Rest of the investigations were within normal limits. Patient started taking Risperidone one week back. On third day an erythematous rash and flaccid blisters appeared on her back and arm. Intake of medication was stopped immediately. The cutaneous rash progressed on to the trunk, face and limbs reaching almost 52% of body surface, blisters appeared progressively on the erythematous areas during the following 2 days. There was >30% skin epidermal

detachment. A calculated scortten 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 risk of infections. Patient was placed on fluidized bed and benefited from supportive and antiseptic measures. Systemic corticosteroids were given. Massive rehydration was undertaken with strict vital monitoring. Over next 48 hours there was involvement of >90% body surface area. The Nikolsky sign was positive. There were erosive lesions of skin and mucosa involving eyes (Figure 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 different degree of acute mucocutaneous reaction that often can be caused by drugs.<sup>1</sup> 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).<sup>3</sup> 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).<sup>7</sup>

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

simply necrosis, following different phases.<sup>10,11</sup>Phase 1 is determined by immunogenic impact of xenobiotics. It involves a lack of balance between activation and detoxification process in keratinocytes. Phase 2 corresponds to early apoptosis. Generation of strongly electrophilic metabolites in TEN keratinocytes is thought to lead to disruption of 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- $\alpha$  and CD95 proapoptotic systems.<sup>11</sup>In late apoptosis(phase 3)the proinflammatory cytokine TNF- $\alpha$  is believed to act as 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.<sup>12</sup> There is currently no specific treatment for TEN. Discontinuation of suspected drug with supportive care(e.g. wound care , hydration, and nutritional support) forms the basis of treatment.<sup>4</sup>Intravenous immunoglobulin therapy (IVIG) is considered by many clinicians as a treatment option, blocking the binding of CD95L.<sup>13</sup>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.<sup>14</sup> 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 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- $\alpha$  and interleukin-6. Few patients have been successfully treated with high dose intravenous NAC in open label studies.<sup>15,16</sup> 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.<sup>17,18</sup> 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 in order to achieve optimal efficacy in the treatment of TEN.

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