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Case Report

Non-steroidal anti-inflammatory drugs induced toxic epidermal necrolysis

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ABSTRACT

This case report presents a 48-year-old woman with a history of chronic kidney disease who experienced toxic epidermal necrolysis (TEN), also known as Lyell's syndrome, an uncommon and severe adverse drug reaction. The TEN was attributed to the use of non-steroidal anti-inflammatory drugs (NSAIDs). Cutaneous involvement exceeded 80% of the body surface area (BSA), encompassing ocular, oral, and nasal mucosa, as well as the trunk, bilateral limbs, and genitalia. Treatment commenced with aggressive fluid resuscitation, the administration of cyclosporine, and meticulous dermal care. The patient was ultimately discharged following approximately one month of intensive therapy.

Keywords: Toxic epidermal necrolysis, NSAIDs, AKI, SCORTEN score

INTRODUCTION

A rare and acutely life-threatening mucocutaneous syndrome, TEN represents the most severe manifestation within the spectrum of severe epidermolytic adverse cutaneous drug reactions. TEN is characterized by extensive dermal-epidermal junction separation, resulting in bullae formation and subsequent desquamation of the epidermis. This widespread cellular demise additionally induces detachment of mucous membranes.[1]

Diagnosis of TEN hinges on epidermal detachment exceeding 30% of total BSA. A less severe variant, Stevens-Johnson syndrome (SJS), manifests with epidermal involvement below 10% BSA. The characteristic clinical presentation of SJS and TEN commences with the development of atypical, dusky macules, progressing to targetoid erythema and bulla formation on these purpuric macules. Additionally, both conditions involve mucosal compromise and epidermal sloughing.[2]

The cornerstone of TEN management lies in supportive care provided within a specialized burn unit. This entails prompt cessation of the offending medication, meticulous fluid resuscitation, implementation of rigorous infection control protocols, aggressive pain management strategies, and meticulous wound care. Debridement of necrotic epidermal tissue and subsequent skin grafting interventions may be necessary in certain cases. Notably, antibiotic therapy should be reserved for situations where demonstrable signs of infection are present.[3]

CASE REPORT

A female patient of age 48 years weighing 60 kg came with the complaints of rashes over face 10 days back which was then followed by progression to whole body. The patient has been previously diagnosed to have chronic kidney disease for which she was on ayurvedic medication. Patient have been taking an unknown drug (Not identified by the patient) since a month for joint pains, after which she developed reddish rashes which

started over face and then advanced to involve the whole body. There was no history of any malignancy, Diabetes mellitus, hypertension and seizures and similar episodes in the past as well as no significant family history. History of hysterectomy 20 years back, ovarian cystectomy in 2018 is listed in the patient's medical history. Upon general examination by the physician, the patient was observed as ill looking, conscious, co-operative and well oriented to time, place and person. Facial edema was noted. Cutaneous assessment shows considerable skin loosening, multiple erosions, multiple bullae present over ankles and skin tenderness. A well-defined erythematous to hyper pigmented macules and coalescing to form patches present over face, trunk, bilateral upper and lower extremities. The oral cavity appears to have erythema and erosions present over oral mucosa, tongue, palate. Crusting over lips and nasal mucosa were marked. Erosions and erythema existed in genital mucosa too. The scalp, hair and nails seemed fine.

These dermal irregularities have covered over 80% of patient's BSA with positive Nikolsky sign. The patient was febrile with all the normal vitals (GRBS 107 mg/dl, Bp 110/70 mmHg and pulse rate 96/min). Based on the evaluation done, the patient is diagnosed with NSAID'S induced TEN. Laboratory tests were ordered.

Figure 1: Multiple bullae, erythema and crusting over lips.

Arterial blood gases parameter reveals hyponatremia (Na^+ 44 mmol/l; Ref 136-146 mmol/l), hypokalemia (k^+ 0.8 mmol/l; ref. 3.4-4.5 mmol/l), bicarbonate levels of 28.1 mmol/l (Ref 136-146 mmol/l), elevated pH, increased partial pressure of O_2 to 131 mmHg (Ref 83-108 mmHg) and decreased partial pressure of CO_2 to 19.1 mmHg (Ref 32-45 mmHg). High Anion gap of 85 mEq/l was simultaneously observed. Complete blood picture shows moderate anemia of hemoglobin 9.6 g/dl (12-15 g/dl). Numbers from renal function test reveals high creatinine and urea level (2 mg/dl; Ref 0.70-1.3 mg/dl and 74 mg/dl; Ref 15-40 mg/dl) respectively. Levels of C - reactive protein were also found to be raised to 70 mg/dl. The SCORTEN score was 3. The patient's mortality rate was determined to be 35.3 percent.[4]

On 1st day of admission, patient's required fluid replacement which was calculated to be 9600 ml/hr. she was prescribed with intravenous: Ringer's lactate, amoxyclav (amoxicillin + clavulanic acid) 1.2 gm BD, paracetamol 1 gm BD, pantoprazole 40 mg OD, pheniramine maleate 4 mg OD/HS, multivitamin OD. Dermatological therapy included banana leaf dressing, saline soaks over lips and eyes, benzocaine gel for oral use 15 min before breakfast, liquid paraffin, and Mupirocin ointment for application over erosions. Saline gargles twice a day and administering refresh eye drops every hour. is advised. Tablet cyclosporine 50 mg twice a day was initiated.

On the 2nd day of admission normal saline was introduced in the treatment. ABG sample were sent and the reports showed improved sodium levels to 123 mmol/l, potassium 2.5 mmol/l and bicarbonate level dropped to 11.4 mmol/l. Creatinine levels get elevated to 2.3 mg/dl after which consultation with a nephrologist was advised. It was also directed in view of metabolic and respiratory alkalosis along with hypokalemia. A diagnosis of TEN with likely acute kidney injury and high anion gap metabolic acidosis was made. Injection sodium bicarbonate stat was ordered. Then tablet sodium bicarbonate at a dose of 500 mg twice a day was included in the treatment.

The patient was then referred to ophthalmic examination which details edematous matting of eye lashes, hazy cornea and sluggish pupil of both eyes. Ciprofloxacin eye drop every 6 hr. was incorporated into treatment. The treatment continued for 27 days during which amoxyclav was stopped on 5th day, injection Piptaz (piperacillin + tozabactum) 4.5 g in 100 ml of normal saline twice a day was started. Skin care regimen was rigorously followed to which chlorhexidine mouth wash twice daily, saline washes for eye drops was added to the therapeutic approach. Tablet riboflavin 1 mg OD was also included. Capsule cyclosporine 100 mg at morning and 50 mg at night was prescribed.

Under these extensive treatment, acute kidney injury resolved and skin tenderness started decreasing significantly. The patient and the care taker were counselled about the adequate intake of 20-25 kcal/kg/day and to consult with physician before taking any pain-relieving medications and gave her a discharge note.

DISCUSSION

TEN manifests as a severe mucocutaneous reaction, occasionally triggered by NSAIDs and a multitude of other therapeutic agents. This life-threatening condition exhibits a mortality rate exceeding 40%. The annual incidence of TEN is estimated to range between 0.4 and 6 cases per million individuals.

A French investigation exploring adverse drug reactions linked to NSAID administration revealed that, relative to other NSAIDs, Nimesulide, ketoprofen, tenoxicam and meloxicam exhibited the highest propensity for inducing hepatic, GI, renal or skin related complications, with this order reflecting both severity and incidence.[5] NSAIDs can cause various skin problems, including serious ones like SJS and TEN. A study by Mockenhaupt et al looked at 373 cases and found that 112 people had taken NSAIDs before. In this group, oxicam NSAIDs had the biggest link to increased risk of SJS/TEN. Out of the other NSAIDs (not oxicams) with enough people who took them, only diclofenac and ibuprofen had a significantly higher risk of SJS/TEN.[6]

In the acute phase of TEN, extensive epidermal detachment manifests as sheet-like denudation. Clinically, TEN presents with confluent purpuric macules or atypical targetoid lesions, accompanied by blistering and erosions exceeding 30% of the BSA. The prodromal phase often features a constellation of symptoms including fever, malaise, anorexia, pharyngitis, headache, and a rash. This exanthem can be morbilliform, characterized by fine, discrete maculopapules, or present as atypical targetoid macules. Notably, TEN is associated with not only cutaneous manifestations but also severe dysfunction in ocular, pulmonary, cardiovascular, gastrointestinal, and renal systems, alongside potential abnormalities in the hematopoietic system.[7] While the hallmark cutaneous manifestation of TEN during the acute phase is extensive sheet-like epidermal detachment, the disease also presents with a range of laboratory and histopathological abnormalities. Anemia, neutropenia, lymphopenia, hypoalbuminemia, and electrolyte imbalances are frequently observed laboratory findings. Histopathological examination typically reveals keratinocyte necrosis, encompassing either partial or complete epidermal involvement. The absence of definitive diagnostic criteria necessitates a reliance on clinical history and a comprehensive laboratory workup for the diagnosis of TEN/SJS.[8]

A recent discovery implicates the HLA loci HLA-A*02:06 and HLAB*44:03 as significant risk factors for severe SJS and TEN manifestations in patients utilizing nonsteroidal anti-inflammatory drugs.[9]

In a study by Hung et al a significantly higher prevalence of chronic kidney disease was observed within the subgroups concurrently receiving allopurinol and NSAIDs. Patients with SJS/TEN exhibited a significantly higher incidence of hyponatremia upon admission compared to the control group. Notably, hypokalemia developed later in the course of the disease, typically within one to two weeks after admission, and was also more prevalent in the SJS/TEN cohort. Intriguingly, both hyponatremia and hypokalemia demonstrated an association with the use of anticonvulsants, allopurinol, NSAIDs, herbal medications, and acute renal failure. The study identified a link between chronic kidney disease and the development of SJS/TEN, as well as an association between CKD and the use of allopurinol or NSAIDs in the study groups. This may be because the predominant effect of CKD makes SJS/TEN patients more susceptible to acute renal failure. The study concluded that skin detachment occurring after certain medications might indicate associated ARF, particularly in CKD patients.[10]

TEN and SJS share a common pathogenetic mechanism involving a T cell-mediated type IV hypersensitivity reaction. This response is initiated by an immunological response to an antigenic drug or complex formed between the drug and host tissue. Several theories attempt to explain the process of T cell stimulation. The hapten/prohapten theory posits that drug metabolites act as foreign antigens, triggering an immune response. The altered peptide model proposes that drugs bind to HLA molecules, altering the presentation of self-peptides on the cell surface, which are then recognized as foreign by T cells. Finally, the pharmacological interaction theory suggests direct binding of drugs to T cell receptors, leading to activation of cytotoxic T cells and the release of cytotoxic mediators like granulysin.

The immune response in TEN and SJS drives a cell-mediated cytotoxic reaction targeted against keratinocytes, leading to widespread apoptosis via intrinsic and extrinsic pathways. Intrinsically, keratinocytes undergo programmed cell death by generating toxic metabolites and reactive oxygen species. Extrinsically, cytotoxic lymphocytes and other immune cells release a panoply of cytotoxic mediators. Interleukin-15 plays a critical role in activating natural killer cells, CD8+ T cells, and other immune effector cells. Elevated levels of Fas-ligand, TNF-alpha, granzyme B, and perforin detected in blister fluid provide further testament to their involvement in the cytotoxic process. In conclusion, the intricate interplay between drugs, immune cells, and potentially underlying genetic susceptibilities precipitates keratinocyte apoptosis and extensive epidermal necrosis, the defining characteristics of TEN and SJS.[11]

The SCORTEN (severity-of-illness score for TEN) score, a prognostic tool for assessing the severity of TEN, evaluates seven risk factors, each assigned a score of 0 or 1. The mortality rate increases from 3.2% with a score of 0-1 to >90% with a score of 5 or more.

Intravenous immune globulin (IVIg) was initially endorsed for preventing keratinocyte apoptosis; however, studies have yielded mixed results regarding its effect on mortality. European guidelines currently advise its early application when superior alternatives are lacking. Cyclosporine has demonstrated a more significant mortality benefit than IVIg, typically administered at a dose of 3 mg/kg over a seven-day period followed by tapering. TNF-α inhibitors like infliximab and etanercept have shown potential in achieving rapid lesion healing

and re-epithelialization, whereas thalidomide, another TNF-α inhibitor, was found to be harmful in trials, leading to increased mortality. Granulocyte colony-stimulating factor (G-CSF) has been noted to assist in recovery and re-epithelialization in severe TEN cases complicated by neutropenia, though the available data is limited. These treatment options highlight the ongoing need for research to establish more definitive therapeutic protocols for TEN.[12] By augmenting the glutathione redox system's buffering capacity, N-acetylcysteine facilitates the elimination of various drugs. Case reports substantiate its potential role in inhibiting NF-kB in some TEN patients. Furthermore, following an SJS/TEN diagnosis induced by a particular drug, it is prudent to avoid structurally similar agents altogether. The safest course of action, particularly in NSAID-induced SJS/TEN, is to restrict all NSAIDs.[13]

CONCLUSION

This case report underscores the successful management of TEN complicated by acute kidney injury. Counselling sessions spearheaded by clinical pharmacists on the prudent use of NSAIDs in the future hold the potential to enhance the quality of patient care significantly as TEN frequently culminates in numerous enduring sequelae, significantly impairing the quality of life of affected individuals. These complications encompass visual acuity deficits, corneal abrasions, photophobia, alopecia, and hyperpigmentation, all of which engender dependency, diminished life satisfaction, and a requisite for rehabilitation. In the context of prescribing NSAIDs, it is imperative to emphasize patient education, particularly regarding the prompt cessation of these agents at the onset of any dermatological manifestations, unexplained pyrexia, or mucosal abnormalities.

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