ORIGINAL RESEARCH PAPER

Volume-8 | Issue-5 | May-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A SEVERE FORM OF TOXIC EPIDERMAL NECROLYSIS [LYELLS SYNDROME] – A CASE REPORT

Plastic Surgery

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ABSTRACT

Toxic epidermal necrolysis (TEN) and Stevens Johnson Syndrome (SJS) are severe adverse cutaneous drug reactions that predominantly involve the skin and mucous membranes. Both are rare, with TEN and SJS affecting approximately 1or 2/1,000,000 annually, and are considered medical emergencies as they are potentially fatal. They are characterized by mucocutaneous tenderness and typically hemorrhagic erosions, erythema and more or less severe epidermal detachment presenting as blisters and areas of denuded skin[1].Lyell's syndrome is an adverse reaction to drugs which, apart from affecting blood and coagulation, mainly targets the cutaneomucous, respiratory,digestive, and urinaryepithelium.[2] Currently, TEN and SJS are considered to be two ends of a spectrum of severe epidermolytic adverse cutaneous drug reactions, differing only by their extent of skin detachment. Drugs are assumed or identified as the main cause of SJS/TEN in most cases.[1].

It may be triggered by infections, but it is believed that at least 80% of cases are caused by medications. The pharmaceuticals worth mentioning are sulfonamides, allopurinol, carbamazepine, phenytoin, and phenobarbital. It is a disease with multisystem impacts, and its clinical presentation includes skin and mucosal changes that affect more than 30% of the total body surface[3].The evolution is accompanied by local complications (superinfections, vicious scars), or general complications (sepsis, multiple organ failure)[4]. We present the case of a patient with drug-induced Lyell's syndrome associated with exposure to a classof nativedrugs at risk of inducing Lyell's syndrome. Supportive therapy, associated with the treatment of cutaneous mucosal lesions, and the treatment of sepsis, were the most important elements that led to a favourable evolution of our case.

KEYWORDS

Toxic epidermal necrolysis (TEN) ; Stevens Johnson Syndrome (SJS)

INTRODUCTION

In 1956 Lyell described the toxic epidermal necrolysis (TEN) about four patients with skin peeling similar to that observed in the burned, evoking epidermal necrolysis toxic origin without assimilating the polymorphe1. Erythema subsequently, it was noted that the same causes could induce both the Stevens-Johnson syndrome (SJS) and TEN and SJS an initial table could grow in TEN. So, SJS and TEN are a very serious illness even variants: toxic epidermal necrolysis (TEN) substantially drug-induced differing only by the extent of cutaneous detachment (<10 per 100 of the total area for SJS. more than 30 p. 100 for TEN. Between 10% to 30% for the transitions the two forms). This is a rare but serious drug eruption, unpredictable occurrence, leads to a destruction of the surface layer of the skin and mucous membranes .Many drugs that may be responsible: Allopurinol, sulfonamides, antiepileptic. The therapeutic management is essentially symptomatic. It resembles that of severe burned through the stop of the suspect medication, fluid and electrolyte intake of quality and prevention and appropriate treatment of the infection[5]. For unclear reasons, it was found that patients with human immune deficiency virus (HIV) have higher risk of developing SJS and TEN compared to un-infected people . Other infections such as Mycoplasma pneumoniae infections and herpes simplex viral infections were linked to SJS and TEN even without previous exposure to medications[6]. The prognosis is severe, evaluated using a specific scale of severity of the disease, the SCORTEN [7]. and nearly 50% of sequelae, particularly eye, in survivors.a. The severe findings of TEN are often preceded by 1 to 2 weeks of fever. These symptoms may mimic those of a common upper respiratory tract infection. When the rash appears it may be over large and varied parts of the body, and it is usually warm and appears red. In hours, the skin becomes painful and the epidermis can be easily peeled away from the underlying dermis [8].bles that of scalding of the skin and is rapidly fatal. It has been difficult to distinguish between TEN and staphylococcal scalded skin syndrome (SSSS), and generalized fixed drug eruption (FDE),TEN continues to be in vogue as a popular caption as was initially described. Toxic epidermal necrolysis (TEN) Lyell's syndrome, therefore, is a fascinating challenge and warrants instant attention.In TENskin rash rapidly coalesces to transform into a.widespread dusky erythema, intense necrosis and epidermal detachment in sheets. It is invariably accompanied by constitutional symptoms and systemic involvement. The withdrawal of the incriminating agent might result in self-limiting disease. TEN closely resembles SJS; however, the body surface area is relatively less extensive in the latter, and mucosal involvement might be reversible[9].The aim of our work is to report the clinical manifestations through an observation and, above all, to draw the attention of the clinician to a syndrome where the precocity diagnosis is a very important step allowing the stop of the drug or incriminated drugs (s), associated with symptomatic treatment[5].

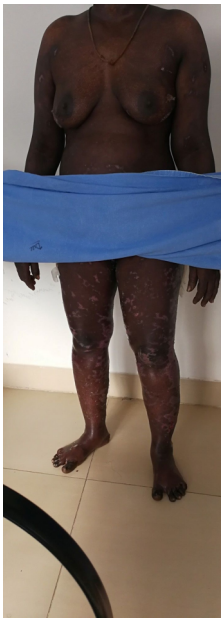
CASE REPORT –

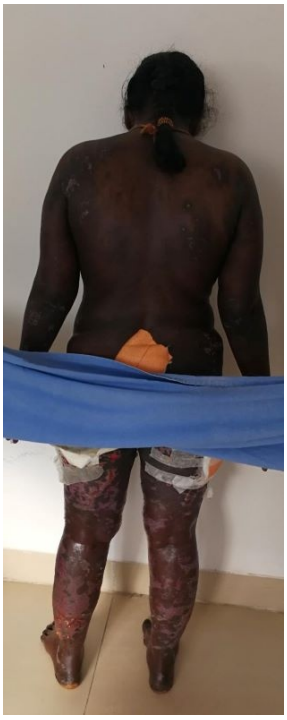
The patient, a 40-year-old female, was admitted to the dermatology department with history of erythematous lesions in the skin and fever for the past one week, with history of taking native medicines containing allopurinol for a period of one week. Patient also gave no history of previous adverse or allergic drug reactions. Plastic surgery consultations were obtained, and the diagnosis of TEN was considered. The patient was transferred to the Department of Plastic Surgery due to the progressive nature of his skin eruption.

The patient developed a high grade fever. On examination, his blood pressure was 140/90Hg, his pulse rate was 122/min, his respiratory rate was 28/min, and his body temperature was 39.8°C. Chest auscultation was normal.A painful, generalized, erythematous maculopapular eruption, with crusts and separation of the skin on his face, oral cavity, neck, chest, back, anterior abdomen wall , both upper and lower limbs involed, and the genital region; Nikolsky's sign was positive. More than 85% TBSA was involved. Skin biopsy from the anterior abdomen wall was sent for HPE and it showed total epidermal destruction and

perivascular lymphocytic infiltration , favouring a diagnosis of Toxic EpidermoNecrolysis.The patient was taken up for emergency wound debridement under anesthesia. The necrotic epidermis was debrided and covered with sterile biological material. The patient developed a high spiking fever. Patient was treated with intra venous antibiotics , fluid resuctiation was done and patient was treated in intensive care unit for a period of one week , the patients general condition was improving and then the patient was transferred to the burns ward.

The patient was treated with intra venous antibiotics , fluid resuctiation and regular dressings were done under anesthesia. On the post op day 25 patient was recovering well and was planned for discharge.





DISCUSSION –

There are several causes of SJS and TEN, but drugs appear to be the most common. However, in some SJS patients, infections, malignancy, and other autoimmune disease may be the cause, while TEN is almost always drug-induced.More than 100 different kinds of drugs have been reported to cause SJS and TEN. It is found that carbamazepine, phenytoin and allopurinol have been strongly associated with SJS and TEN.[10]

The pathophysiology of the TEN is not yet fully elucidated and is a subject of controversy. The time between the administration of the triggering agent and onset of symptoms is less in TEN recurrences, strongly supports the existence of primary sensitization and immunological memory. The occurrence of TEN in individuals with auto immune diseases and with particular antigen markers of the HLA system also favors the immunological role in the pathogenesis.

On the other hand, one theory suggests a direct “toxic” effect by medication or a metabolite triggers cell death in epidermal keratinocytes. Alternatively, the drug triggers an immune reaction and the activated immunocytes mediate the cytopathic effects in much the same way that epidermal killing is seen in acute cutaneous graft versus host disease.[11]

Characteristic histologic features include extensive keratinocyte death with separation of the epidermis from the dermis at the dermoepidermal junction. A paucicellular infiltrate, in which macrophages and dendrocytes predominate, has been commonly described. TEN has been characterized pathologically by an increased ratio of dermal dendrocytes to dermal lymphocytes. The death of keratinocytes has been shown to be through apoptosis.[11]

The following criteria must be fulfilled for a case to be diagnosed as TEN.

1. Bullae or erosions involving more than 30% of body surface area or three different anatomical sites.
2. Skin peeling in sheets of more than 3 cm.
3. Involvement of skin not exposed to sunrays.
4. Involvement of mucous membrane frequently.
5. Skin tenderness within 48 hrs of rash.
6. Biopsy confirmation within 48 hrs.
7. Fever.
8. Bullae arising on an erythematous background.
9. Exclusion of SSSS[11].

TEN is characterized by extensive detachment of the epidermis secondary to necrosis. The pathogenesis is still not well understood,

but it is based on a delayed hypersensitivity reaction to drugs in individuals with greater genetic predisposition. After contact with the causative agent, prodromal symptoms (fever, rhinitis, cough, chest pain, myalgia, anorexia, and asthenia) begin. They precede the onset of mucocutaneous lesions characteristic of the acute phase, which lasts 2-12 days. Cutaneous involvement is marked by an itchy, painful rash that primarily affects the face and upper torso, with craniocaudal progression. Erythema may be macular with irregular contours and a darker center, reaching its largest size after three days1. The culmination of the process is the characteristic denudation of the necrotic epidermis, which is marked by the detachment of sheets. The epidermis exhibits serous, flaccid, and confluent blisters that burst and open, giving the patient the appearance of having a large burn. The Nikolsky sign is positive, and mucosal lesions appear before epidermal necrosis with erosion and peeling of conjunctival, oro-pharyngeal, nasal, esophageal, urethral, anal, vaginal, and perineal mucosa. It is a self-limiting disease, but complications are serious and potentially life-threatening. Secondary infection is the most severe complication, and sepsis is responsible for over 50% of the cases of death. The loss of the skin barrier enables bacterial invasion of exogenous or endogenous origin. Psychomotor agitation and confusion are not uncommon and are usually indicative of hemodynamic complications and sepsis. Ocular involvement may be present in 39% to 61% of cases and includes complications such as corneal ulcers, anterior uveitis, and panophthalmitis. Respiratoru changes are common, and 10 to 20% of patients may require artificial ventilation. Gastrointestinal adhesions are not uncommon, nor are urinary incontinence, vaginal stenosis, renal tubular necrosis, renal failure, skin ulcers with re-infection, and non-esthetic scars. In 90% of cases, blood disorders such as anemia and leukopenia with lymphopenia are due to a temporary depletion of CD4 + T lymphocytes, and in 30% of cases, neutropenia is usually associated with the onset of sepsis and poor prognosis. Thrombocytopenia is more uncommon, and occurs in 15% of patients. Neurological abnormalities found in the acute phase of the disease are not described in the literature. Clinically, this patient exhibited signs of impairment of the posterior fossa, brainstem, basal ganglia, and cerebral cortex (seizures), all of which suggested posterior reversible encephalopathy syndrome (PRES) as a differential diagnosis.

DIFFERENTIAL DIAGNOSIS –

Erythema multiforme (EM)

Is a skin disorder that share some features of the TEN making it sometimes diffi cult to differentiate between two conditions. There are some criteria's which would differentiate them.

EM is characterized by presence of localized lesion <3 cm wide. It may or may not present as target lesions. Covers <20% of the body.Absence of mucosal involvement.

SJS

It is almost similar to the TEN except it covers <10% total body surface area. Individual lesions are <3 cm wide.

SSSS

Skin infection caused by certain strains of Staphylococcal aureus due to release of certain specifi c exotoxins. This syndrome is commonest in infants and neonates. It has clinical spectrum similar to TEN, its distinctive featureincludes absence of painful experiences and mucosal involvement. The histological difference is partial epidermal necrosis with intra epidermal cleavage at the granular layer level.

Scarlatiniform rash

It is usually caused by Group A Streptococcus or S. aureus.
It can induce wide spread erythema, which is more marked at the fl exural folds, with possible desquamation of the digital pulps, pharyngitis and strawberry like tongue.

Toxic shock syndrome

Is caused S. aureus, is characterized by diffuse erythema with desquamation particularly over the palms and soles, fever and systemic involvement that rapidly progress to shock.

Kawasaki disease

Multi system disease of unknown etiology that affects the children <5 years. It is characterized by fever, polymorphic skin rash, conjunctivitis and tongue fi ssures which is some time mistaken for TEN.[1]

MANAGEMENT –

ThE aim of managing TEN is limiting disease progression and preventing infection:

1) An acute awareness of the condition is important so that appropriate drug choices can be made recognizing their potential for initiating this complication. Also prophylactic sulfonamide anti-biotics in HIV patients on ARVs should be stopped as soon as CD4 counts are seen to be rising;
2) Treatment as for an acute burn -admission to a burn wound centre or specialized burn section if possible; resuscitative measures; anti coagulation with low dose heparin should be considered in all cases as one would when treating comparable burn injuries;
3) Initial and continued debridement is controversial. In most cases, the nature of the pathology appears to suit a mechanical gentle wash rather than an aggressive debridemen
4) Many cases will be able to be dressed directly without debridement following a gentle cleansing in the ICU/high care environment. The anticoat dressing should applied as soon as possible. Initial application of an hydrogel may facilitate the application of the Acticoatdressing.Thus the amount of exudate, anatomic areas involved, and nature of the wound will determine which Acticoat dressing would be used. The ideal situation is changing the dressing every 3rd day (or longer) if possible. This has distinct advantages of encouraging healing with minimum exposure of the wounds. It is also advantageous in terms of pain control, an exceedingly important component of the healing process. A secondary absorptive dressing is applied if deemed necessary;
5) The wound should be assessed to be deeper (deep partial thickness) or in contracture prone anatomic areas, a biologic skin substitute is an excellent addition to the process. This aids in dermal regeneration and can avoid potential scarring and contractures in anatomically prone areas. Additionally, a biologic skin substitute also reduces exudate loss, reduces pain and decreases the number of dressings, so it may be chosen as a primary dressing in combination with Acticoat in many cases even where depth is not in question, but where anatomic areas are prone to contractures (neck ,hands, feet, elbows etc);
6) The combination dressings are changed when they appear saturated with wound exudate or if the wound appears to have dried. The regime is continued until 90% healing is achieved. Most of these areas may then be left exposed with moisturizing agents used to prevent dessication;
7) Sytemic therapeutic interventions are applied on an individual basis according to circumstances. This includes intravenous anti-biotics, blood replacement and systemic respiratory or cardiac support agents (inotropes, volume expanders, diuretics etc). IVIG use is still undecided;
8) Enteral feeds are preferred to parenteral feeds[12]

CONCLUSION –

TEN is a devastating disease with significant mortality if not diagnosed and managed early and aggressively. It is likely that with more immune compromized patients as a result of disease or treatment modalities, increasing numbers of TEN are likely to be seen.

In keeping with newer strategies to influence systemic outcome by targeting the local wound interface, dressings are being used not only to aid in healing, but to control sepsis and to decrease the destructive inflammatory component of the disease. NCS is one such agent that has an effective anti-bacterial spectrum, but also has the potential of modulating the protease activity influencing the inflammatory component of the disease. Together with biologic skin substitutes it can serve as an effective means to promote healing, control pain and prevent contractures in a potentially devastating disease.[12].

After recovery, patients should be advised to avoid not only the suspect drug(s), but also chemically related compounds.[9].

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