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Case Report

Amikacin induced Stevens Johnson syndrome and toxic epidermal necrolysis overlap: a rare case report

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ABSTRACT

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are the most severe adverse drug reactions. They are characterized by necrosis and epidermal release in vesicobulosa skin, mucous orifice, and eyes, with more severe general symptoms. SJS/TEN-overlap syndrome is the term used to characterize situations where 10–30% of the body skin area is detached. TEN or SJS is one of the deadliest dermatological catastrophes. Despite being a rare condition, it frequently has a high death rate. Different types of purpuric macules or rounded patches with mucosal lesions are characteristic features of these type 3 hypersensitivity reactions. We are presenting a case of 50-year-old female patient brought to hospital on account of multiple black to red coloured raised lesions over body in the last 8 days. Patient was asymptomatic in the last 8 days after that patient noted red coloured lesions first over face followed by lower back, upper limb, lower limb followed by itching and Jiburning sensation all over the body. The patient had symptoms such as redness of eyes in the last 3-4 days, burning sensation and ulcers in mouth in the last 3-4 days. These symptoms developed day after she received amikacin. She was diagnosed with SJS-TEN overlap. This case highlights the precipitant of antibiotics for SJS. She was recovered completely after stopping the causative drug and treatment with Immunoglobulin with other symptomatic measures. The causative drug was found to be Amikacin and medicine taken for comorbid conditions like epilepsy, hypothyroidism and hypertension. Rarely, amikacin has been linked to a range of drug hypersensitivity reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and overlap between the two conditions.

Keywords: Stevens-Johnson syndrome, Toxic epidermal necrolysis, Antibiotics

INTRODUCTION

Stevens-Johnson syndrome (SJS) is an acute inflammatory vesiculobullous reaction of the skin, the mucosa of the ocular surface, the oral cavity, and of the genitals; its severe phenotype is called toxic epidermal necrolysis (TEN).[1] TEN and SJS are regarded as delayed-type hypersensitivity reactions to medications. They are actual medical emergencies, and survival depends on early detection and effective treatment.[2] SJS and TEN are characterized by detachment of the epidermis and mucous membrane, both are rare severe cutaneous adverse reactions. SJS/TEN can be life-threatening, with mortality rates between 4.8% and 14.8%.[3]

TEN or SJS is one of the deadliest dermatological catastrophes. Despite being a rare condition, it frequently has a high death rate.[4] In the SJS-TEN overlap category, the epidermal detachment is 10-30% of the total BSA.[5] Only those who are vulnerable can experience

unpredictable hypersensitivity reactions, which can be brought on by non-immunologic or immunologic (allergic) processes. Based on the degree of skin detachment, SJS/TEN can be classified into SJS, SJS-TEN overlap, and TEN. SJS is defined as skin involvement of <10%; TEN is defined as skin involvement of >30%; SJS-TEN overlap is defined as 10-30% skin involvement.[6]

The symptoms of SJS/TEN, which are exceedingly rare but potentially fatal conditions, include a sudden, high fever, evidence of systemic poisoning, and extensive skin and mucosal epidermal necrosis. The skin region affected varies, and 74% to 94% of the SJS/TEN cases are caused by an infection or a history of medication.[7] The two classes of medications that cause drug hypersensitivity reactions the most frequently are non-steroidal anti-inflammatory medicines and antibiotics, particularly beta-lactams.[8] Because SJS and TEN are caused by a specific, genetically defined deficit in the individual's ability to detoxify harmful reactive drug metabolites, they are categorized as non-immunological epidermal drug responses. This is because they involve the absence of an enzyme or protein.[9] Oral involvement is the most prevalent, up to 100% of cases resulting in mucositis and ulceration.[10]

Etiology

Drug hypersensitivity and its genetic components are complicated topics that have been researched across a range of demographic and ethnic groups.[11]

The following drugs were listed as the main ones related to the occurrence of SJS and TEN, based on RegisSCAR/EuroSCAR files.

High risk includes phenobarbital, phenytoin, lamotrigine, nevirapine, sulfasalazine, oxicam-derived nonsteroidal anti-inflammatory medications (e.g., meloxicam), carbamazepine, cotrimoxazole, and other sulphonamides.

Moderate risk includes tetracyclines, cephalosporins, macrolides, quinolones, and nonsteroidal anti-inflammatory medications derived from acetic acid, such as diclofenac.

Low risk includes beta-blockers, calcium channel inhibitors, thiazide diuretics, sulfonylurea antidiabetics, angiotensin-converting enzyme inhibitors, insulin, and nonsteroidal anti-inflammatory medications derived from propionic acid (e.g., ibuprofen).[12]

Clinical features

Fever, upper respiratory tract symptoms, and conjunctivitis that resemble a febrile illness of infectious etiology are the first signs and symptoms, or prodrome. The separation of the nasal, oropharyngeal, conjunctival, and anogenital mucous membranes comes next. Usually, there are multiple mucous membranes involved. Pain and a burning feeling are often present in conjunction with cutaneous lesions, which can manifest as flat, typical or atypical target lesions, or as dark, erythematous macules or purpura. 60–100% of SJS/TEN patients had acute ocular involvement, which can vary from conjunctival hyperemia to nearly complete sloughing of the ocular surface, involving the edges of the eyelids and tarsal conjunctiva.[13]

Risk factors

SCORTEN score is an illness severity score that has been developed to predict in SJS and TEN cases. One point is scored for each of the seven criteria present at the time of admission.

Table 1: Scorten scale.

Risk factor	0	1
Age (in years)	<40	>40
Associated malignancy	No	Yes
Heart rate (beats/min)	<120	>120
Serum BUN (mg/dL)	<27	>27
Detached or compromised body surface	<10%	>10%
Serum bicarbonate (mEq/L)	>20	<20
Serum glucose (mg/dL)	<250	>250

The risk of dying from SJS/TEN depends on the score.

SCORTEN 0-1 >3.2%

SCORTEN 2 >12.1%

SCORTEN 3 >35.3%

SCORTEN 4 >58.3%

SCORTEN 5 or more >90%.

Pathophysiology

Many stimuli, mostly medicines thus/or their metabolites, but also infections or cancers, can trigger T-cell activation in SJS and TEN and cause unintentional immunological activation. One popular hypothesis on T-cell activation is known as the prohapten idea. A new antigen can be created when a drug or one of its metabolites binds to a host protein. The fast commencement of keratinocyte cell death via apoptosis, which causes the epidermis and dermis to separate, is a morphological characteristic shared by both SJS and TEN. The pathophysiology of keratinocyte death during TEN appears to be aided by inflammatory cytokines, the death receptor Fas, and its ligand FasL, according to recent data. Intravenous immunoglobulins (IVIG), which have been demonstrated to contain naturally occurring anti-Fas antibodies and antagonistic monoclonal antibodies to Fas can both be used to block the final stage of TEN's epidermal detachment, which is Fas-mediated keratinocyte apoptosis.[13]

Diagnosis

The presence of characteristic mucocutaneous lesions is typically used to make the clinical diagnosis of SJS. In general, skin samples are used to confirm the diagnosis, which usually show necrotic spinous layer keratinocytes and basal layer keratinocytes vacuolized in relation to lymphocytes along the dermal-epidermal interface. Apoptosis and necrosis of keratinocytes, dermoepidermal separation, and lymphocytic infiltration of perivascular areas are the characteristic histological features of SJS. More popular lesions may show signs of intraepidermal vesicles and papillary dermal edema. Toxic epidermal necrolysis is commonly identified by the presence of subepidermal blistering and full-thickness epidermal necrosis, which may be present in severe cases. Biopsies should be submitted for both routine histology and direct immunofluorescence investigations in order to differentiate this illness from autoimmune blistering disorders.[14]

Management

Early diagnosis of the illness, stopping any suspected drug use, starting supportive therapy right once, making necessary referrals, starting targeted therapy, managing any consequences, and preventing further episodes are all crucial components of management. Tumour necrosis factor-α inhibitors, intravenous immunoglobulin, cyclophosphamide, systemic corticosteroids, cyclosporine, and plasmapheresis are among the immunomodulatory therapies. The cornerstones of SJS/TEN treatment are supportive care and withdrawal of the offending agent. While there is still debate over the best supplementary therapy, treatments like intravenous immunoglobulin (IVIg) and corticosteroids are frequently used.[15] One of the most often given antibiotics is macrolides. Their use has been linked in a number of studies to TEN and SJS.[16] In clinical practice, persistent SJS/TEN overlap is an uncommon condition. For medication withdrawal and the avoidance of potentially lethal consequences like sepsis, prompt clinical recognition is crucial.[17] Therefore, as advised by the World Health Organization, health professionals have an obligation to swiftly and effectively notify any incidence of adverse medication reactions.[18]

CASE REPORT

We report a case of 50-year-old female patient brought to hospital with chief complaints of multiple black to red coloured raised lesions over body in the last 8 days. Patient was asymptomatic since 8 days after that patient noted red coloured lesions first over face followed by lower back, upper limb, lower limb followed by itching and burning sensation all over the body. The patient had symptoms such as redness of eyes since 3-4 days, burning sensation and ulcers in mouth since 3-4 days. These symptoms developed day after she received amikacin.

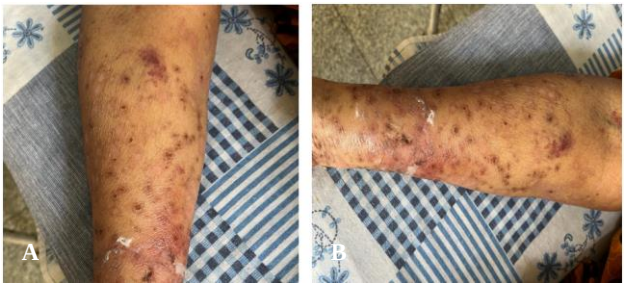

Figure 1 (A and B): Multiple black to red coloured raised lesions on the upper limbs.

The patient had a history of high grade fever along with chills for which she approached a local doctor. She was prescribed with injection ceftriaxone and amikacin for three days twice a day. Soon after the administration of amikacin, the patient developed reddish lesions associated with itching all over the body (limbs, trunk, face and eye lids). Then patient was taken to a different hospital and treated with amoxicillin clavulanic acid 375 mg bd, tab. Fexofenadine and pramoxine and zinc acetate lotion for 3 days; however, there was no improvement.

The patient has a history of hypothyroidism, epilepsy, and hypertension. She was having epilepsy for the past 15 years, for which she was on sodium valproate 500 mg, lamotrizine 250 mg, and aspirin 75/20. For hypothyroidism, she takes thyronorm 100 mg. For hypertension she takes metoprolol 25 mg and amlodipine 5 mg for three years.

The patient was conscious and coherent and was observed to be afebrile. Pulse rate measure as 70 beats per minute, blood pressure was observed as 110/70 mmhg. On examination, P/A is soft and CNS was NFND. Blood gas values are observed as increased PH, decreased PCO2 values and electrolyte imbalance, decreased sodium and chloride values in the blood. Cutaneous examination revealed multiple well-defined erythematosus dusky red to black macules to plaques noted all over the body. Few fluids filled blisters seen over limbs and back.

The blood reports revealed decreased levels of RBC and HGB, increased levels of WBC. Laboratory results on admission revealed WBC 13.74, RBC 3.45 million RBC/ MCL, hemoglobin 12.2g/dl, blood urea 40mg/dl, aspartate amino transferase (AST)-69, alanine amino transferase (ALT)-60, creatine-1.53, sodium-116, potassium-4.3, chlorine-62.

Considering the clinical presentation and involved total body surface area the patient was diagnosed with a suspected case of amikacin induces SJS - TEN overlaps.

SCORTEN scale represents severity of illness score for toxic epidermal necrolysis. By using this criteria the patient was diagnosed as Stevens – Johnson syndrome/ toxic epidermal necrolysis

Table 2: SCORTEN scale.

Risk factors	Reference	Score
Age	<40 years	1
Associated malignancy	No	0
Heart rate (beats/min)	<120	1
Serum BUN (mg/dL)	<27	0
Detached or compromised Body Surface	<10%	0
Serum bicarbonate (mEq/L)	>20	0
Serum glucose (mg/dL)	<250	1

Prognosis was assessed using score of TEN (SCORTEN) criteria which conferred a score of 3 for the index case. The mortality risk was estimated to be 32.4 %.

The patient was managed with

- Glucocorticoids, Inj. Dexamethasone 1cc twice a day to treat allergies.
- Antihistamines, Inj. avil 2cc twice a day for 14 days to treat drug rashes and allergic conjunctivitis
- Antipyretics, Inj. pcm 1 GM twice a day to treat high grade fever
- Antibiotic, Inj. amoxiclav 1.2 gm twice a day to treat several bacterial infections.
- Proton pump inhibitor, Inj. pantop 40 mg twice a day is to reduce acids produce in the stomach.
- Local anaesthetic, Benzocaine ointment for oral mucosal application taken before food which acts as topical Painkiller.
- Corticosteroid, 0.1% triamcinolone cream after food for oral mucosal application to treat mouth sores.

DISCUSSION

SJS caused by Amikacin research on TEN overlaps, an uncommon hypersensitivity reaction, was quite limited. The purpose of this study is to represent a case on SJS. SJS caused by drugs is known, with antibiotics being the primary cause of the majority of instances. Positive results are prompted by early diagnosis, fast identification, and withdrawal of the causing medications.[19]

The patient has a history of hypothyroidism, epilepsy, and hypertension. With epilepsy for 15 years, using sodium valproate 500mg, lamotrizine 250mg, and ecosprin 75/20; hypothyroid a few months ago, receiving thyronorm 100 mg; and having high blood pressure for 3 years, taking metoprolol 25 mg and amlodipine 5mg. The patient was with high grade fever along with chills then patient received injection monocef and amikacin for three days twice a day. After patient received amikacin patient developed reddish lesions associated with itching over body (limbs, trunk, face and eye lids). Patient is diagnosed with amikacin induced SJS and TEN overlap. Amikacin belongs to the class of aminoglycoside antibiotics. The term “aminocyclitol” refers to the six-membered ring that is a necessary component of all aminoglycosides and contains amino group substituents. The glycosidic linkages that form between the aminocyclitol and two or more sugars, either amino-containing or not, result in the descriptor aminoglycoside. Two classes of aminoglycosides are distinguished: (A) the group of streptidines, such as streptomycin; (B) the group of desoxystreptamines, such as neomycin, kanamycin, amikacin, gentamicin, and tobramycin. Nephrotoxicity and ototoxicity are the most common and significant side effects of aminoglycosides. Hypersensitivity reactions could, nevertheless, happen. >2% of treatments result in allergic reactions to neomycin and streptomycin, 0.1–2% to gentamicin and amikacin, and 0.1–0.5% to kanamycin. Because aminoglycosides’ chemical structures are similar, they frequently exhibit cross-reactivity. In the deoxystreptamine group (gentamicin, tobramycin, neomycin, amikacin, kanamycin, plazomicin, and paromomycin), cross-reactivity is close to or greater than 50%. 65% of patients with neomycin allergies experienced a cross-allergic response to tobramycin during patch testing. Consequently, if a patient has a history of known hypersensitivity to another deoxystreptamine-containing aminoglycoside, then all deoxystreptamine-containing aminoglycosides should not be administered.[20]

According to Al-Quteiment in 2016 and Vijendra in 2013, 50% of TEN patients would experience late ocular problems, such as severe dry eyes, trichiasis, symblepharon, distichiasis, vision loss, entropion, ankyloblepharon, lagophthalmos, and corneal ulcers. According to Lihite, 4 a thorough clinical history of the patient is required to ascertain whether the medication was present in the body at the time of the adverse reactions onset. Early detection and quick corticosteroid treatment might enhance the result. Due to the diversity and infrequency of adverse systemic responses to AEDs, doctors who start patients on AEDs should advise them to contact them if they have any new or strange symptoms. In 2013, Elazzazyin wrote. Administration of fluids and nutritional supplements intravenously is important in order to avoid dehydration and sepsis. Oral ulcerations are very common symptoms which make it difficult in taking of food orally. Accurate diagnosis of the illness is crucial since doctors would never understand mouth ulcers. For certain other ailments, patients should also refrain from evaluating it for SJS. Plasmapheresis would help in draining of the culprit Drug from the body, thus bringing much recovering States. Given that the patient’s condition nearly mimics a burn state, treatment in an intensive burn care facility would be quite useful. Additionally, it is crucial to educate patients about the potential for harmful medication reactions. Myocarditis can occur infrequently, either with or without SJS. Furthermore, in such potentially fatal situations, it is crucial to properly inform the patient about the use of drugs. Frequent observation of these ADRs, along with patient and physician education, can aid in early diagnosis

and stop the emergence of serious side effects from these unusual reactions.[21]

According to Sanmarkan et al's study, men are more likely than women to have SJS in contrast; our patient is a woman.[22]

CONCLUSION

SJS and TEN are the most severe adverse drug reactions characterized by necrosis and epidermal release. We encountered a patient who was diagnosed with Stevens-Johnson syndrome SJS and TEN overlap. She was recovered completely after stopping the drug in addition to treatment with Immunoglobulin with other symptomatic measures. The culprit was found to be Amikacin and medicine taken for comorbid conditions like epilepsy, hypothyroidism and hypertension. Amikacin induced SJS and TEN overlap is a very rare adverse drug reaction. Frequent observation of these ADRs, along with patient and physician education, can aid in early diagnosis and stop the emergence of serious side effects from these unusual reactions. Corticosteroids are a choice of therapy for SJS in most of the cases. SJS and TEN are severe ADR usually caused By NSAIDs, antibiotics and antiseizure drug and the overall cost of management is higher than other ADRs. We hope that sharing the patient's case profile will broaden the body of knowledge already in existence.

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