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Original Research Article

Clinical Study of Severe Cutaneous Adverse Reactions to Drugs

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Abstract:

Background: Adverse drug reaction is defined as 'an undesirable clinical manifestation resulting from administration of a particular drug; this includes reaction due to overdose, predictable side effects and unanticipated adverse manifestations'. 1 of every 1000 hospitalized patients has a serious cutaneous drug reaction. SJS and TEN are associated with severe morbidity and mortality. The fatality rate in SJS is reported to be 5-10%, while in TEN it is reported to be 25-30%. So, the following study shall thus be a sincere effort to explore more about the adverse drug reactions.

Objectives: To study the different clinical patterns of SCAR, and to identify the offending drugs causing different types of SCAR.

Methods: The study has been conducted in the department of Dermatology, Silchar Medical College & Hospital, and Silchar, Assam over a period of one year extending from 1st June 2018 to 31st May 2019 after approval from the Institutional Ethics Committee (IEC) and after obtaining informed consent from the patients.

Results: Out of the total 57,712 new patients attending the Department of Dermatology, Silchar Medical College & Hospital, and Silchar during the period from 1st June 2018 to 31st May 2019, 31 patients were diagnosed as having severe cutaneous adverse reactions due to drugs. Out of a total of 31 patients, 18 patients (58.06%) were male, while 13 patients (41.94%) were female with a male: female ratio of 1.38:1. In this study, the most common clinical pattern was the SJS-TEN part of the spectrum (64.52%) with SJS 35.48%, SJS/TEN overlap 6.45%, TEN 22.58%. In present study, Antimicrobials were the most common causative drugs (41.93%) followed by Anticonvulsants (35.48%) followed by Antipyretic analgesics (16.13%). The most common drug causing SCAR in this study was Carbamazepine (22.58%).The duration from the drug administration to cutaneous reactions (Reaction time) ranged from 12 hours to 60 days in this study. Shorter duration of 12 hours was seen in 1 case of TEN associated with re-exposure of the same drug Cotrimoxazole. Shorter duration of 12 hours was also seen in 2 cases of AGEP. Skin, oral and conjunctival mucosa were involved in 6 (54.54%) patients of SJS, 1 (50%) patients of SJS/TEN overlap, 2 (28.57%) patients of TEN and 2 (40%) patients of DRESS. Nikolsky's sign was positive in all patients of TEN, SJS-TEN overlap and 2 cases of SJS which is per se Pseudo-Nikolsky's sign.

Conclusion: Severe cutaneous adverse reactions are highly troublesome and fatal conditions and are to be treated as an acute emergency, preferably in a Dermatology ICU. A sound knowledge of different clinical patterns and common causative drugs may lead to early suspicion and recognition so that the offending drug can be recognized early and stopped as soon as possible to limit the morbidity and mortality.

Keywords: Stevens Johnson Syndrome**,** Toxic Epidermal Necrolysis**,** Drug Rash with Eosinophilia and Systemic Symptoms**,** Acute Generalized Exanthematous pustulosis.

Introduction

Adverse drug reaction is defined as 'an undesirable clinical manifestation resulting from administration of a particular drug; this includes reaction due to overdose, predictable side effects and unanticipated adverse manifestations'. [1] ACDR occurs with varying severity. The clinical pattern of drug reactions can vary from transient erythema to the life-threatening severe cutaneous adverse reactions (SCARs) that include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) as per Regiscar group. [2]

The term severe cutaneous adverse reactions have been proposed that share the following criteria [3]:

1. Being severe requiring hospitalization and usually associated with significant mortality and morbidity.
2. Nonpredictable (idiosyncratic, and probably of immunological mechanism).
3. 3) Often induced by medications.

1 of every 1000 hospitalized patients has a serious cutaneous drug reaction. [4] SJS and TEN are associated with severe morbidity and mortality. The fatality rate in SJS is reported to be 5-10%, while in TEN it is reported to be 25-30%. [5]

Material and Method

The clinical observational study (cross sectional study) has been conducted in the department of Dermatology, Silchar Medical College & Hospital, Silchar, Assam over a period of one year extending from 1st June 2018 to 31st May 2019 after approval from the Institutional Ethics Committee (IEC) and after obtaining informed consent from the patients. All total of 31 patients who satisfied the above criteria were taken into the study.

Inclusion criteria:

All patients attending the Dermatology department (either self-presenting or referred by other departments of this institution) were screened and recruited if they presented with visible skin lesions of Severe Cutaneous Adverse Reactions with definite history of systemic drug intake by prescription or non-prescription, irrespective of age and sex after taking written informed consent.

Exclusion criteria:

1. Patient with incomplete drug history.
2. Patients giving history of use of Topical medications.
3. Patients giving history of intake of Indigenous (Ayurvedic, Homeopathic and Herbal) medications.
4. Patients who did not give consent for the study.
5. Patients on Anti -retroviral drugs were also not included as HIV positive individuals are more prone to develop drug reactions, if so the result will not be reflective of general populations.

A detailed history was elicited in each case regarding age, sex and occupation with a particular reference to cutaneous complaints including lesion type, onset, duration, evolution and progression. Past history and associated comorbidities were also recorded on a predesigned pro forma. General physical examination, systemic examination, and a detailed mucocutaneous examination of all patients were carried out after taking consent. Routine laboratory investigations including serology for hepatitis B, hepatitis C, and HIV were also conducted. Diascopy and dermoscopy wherever needed were used as a means of examination. Skin biopsy was performed in cases of a diagnostic dilemma. Diagnosis of AGEP was done by Euro SCAR study [6]. Diagnosis of DRESS was done by Regi SCAR criteria scoring system.[7] SJS-TEN was diagnosed on clinical grounds. Relevant bedside tests, laboratory tests and special tests were done. This assessment was done by criteria provided by Naranjo CA et al [8]. As per a study to judge effectiveness of different algorithms used to evaluate adverse drug reactions by Michel DJ and Kondel LC [9] concluded that, "The simpler and less time-consuming Naranjo algorithm compared favorably with the Kramer algorithm in scoring ADRs; more data are needed to support the use of the Jones algorithm.'' (Kramer algorithm by Kramer MS et al) [10] and (Jones algorithm by Jones JK). [11] Rechallenge is defined as the readministration of a drug suspected to be a possible cause of an adverse reaction and which has been subsequently discontinued (Stephens M-1983). [12] In this study, rechallenge was not done as in severe reactions, establishing cause with certainty may be extremely difficult as conducting oral provocation tests would be dangerous and unethical. [1,13]

Statistical analysis

The recorded data was compiled and entered in a spread sheet (Microsoft Excel) and then exported to the data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Variables were summarized as frequencies and percentages. Graphically, the data was presented by bar and pie diagrams. A P value of less than 0.05 was considered statistically significant.

Results and Discussion

Out of the total 57,712 new patients attending the Department of Dermatology, Silchar Medical College & Hospital, Silchar during the period from 1st June 2018 to 31st May 2019, 31 patients were diagnosed as having severe cutaneous adverse reactions due to drugs. Thus the overall incidence of SCARs amongst the patients found during the period was 0.54 per 1000 patients attending Dermatology department. Grando LR et al [14] in 2014 reported an incidence of 0.33 per thousand populations. Loo CH, Tan WC et al [15] in 2018 reported an incidence of 0.3.

Sex Ratio

In this study, males outnumbered females. Out of a total of 31 patients, 18 patients (58.06%) were male, while 13 patients (41.94%) were female with a male: female ratio of 1.38:1. There are various studies on the sex incidence of SCARs. The result of the present study is comparable to the following studies – According to some studies, Sashidharanpillai et al [16] in 2015 found M: F ratio of 1.5:1. Sharma R et al [17] in 2017 reported

M:F ratio of 1.59:1. However, in some studies females were predominant population. Shrestha DP et al [18] in 2005 reported male and female ratio of 1:2. Devi K et al [19] in 2015 reported the male and female ratio as 1:3.13. This may be attributable to the geographical variation and variation in health seeking behavior.

Age Group

In this study, the highest number of patients found in the age group of 31-40 years (25.81%) followed by 0-10 years and 51-60 years with a percentage of 16.13%. The age group ranged from 2-76 years. In other studies, Devi K et al [19] in 2015 reported the most common age group was (21-40) years. Sharma R et al [17] in 2017 reported the most common age group was (21-40) years. It is evident that the result of this study is comparable with the above mentioned studies. However, Sashidharanpillai S et al [16] in 2015 reported the highest number of patients in the age group of 46-60 years. This disparity may be due to geographical variation.

Clinical (Morphological) Patterns

In this study, the most common clinical pattern was the SJS-TEN part of the spectrum (64.52%) with SJS 35.48%, SJS/TEN overlap 6.45%, TEN 22.58%. Chowdhury MNG et al [20]-(2016), Sharma R et al [17]-(2017), Misirlioglu D et al [21]-(2017), Loo CH et al [15]-(2018) all found similar results. However, in this study, the second most common pattern was AGEP (19.35%) followed by DRESS (16.13%). There was no correlation with the above studies. All the above studies found more DRESS cases followed by AGEP. This might be due to regional variation and also because AGEP is a newer entity thus, more and more cases are being diagnosed recently. The other reason for this disparity might be due to the fact that most of the studies mentioned above are retrospective studies of longer duration. Results are depicted in Table 1.

Major Group of Drugs Responsible for SCARs

In present study, Antimicrobials were the most common causative drugs (41.93%) followed by Anticonvulsants (35.48%) followed by Antipyretic analgesics (16.13%). However, Grando L et al [14] -2014, Chowdhury MNG et al [20]-2016 found Anticonvulsants to be the most common causative drug.

Most Common Drug Causing SCAR

The most common drug causing SCAR in this study was Carbamazepine (22.58%). Grando LR et al [14] in 2014, Chowdhury MNG et al [20] in 2016, Misirlioglu D et al [21] in 2017 also found carbamazepine as the most common drug. Devi K et al [19] - 2015 and R Sharma et al [17] - 2017 found Phenytoin as the most common causative drug of SCAR. Phenytoin (12.9%) was the third most common causative drug found in this study. Oh H et al [22] - 2019 found Amoxycillin/Clavulanic acid as the most common causative drug. Amoxycillin/Clavulanic acid (16.13%) was the second most common causative drugs found in this study as shown in figure 1.

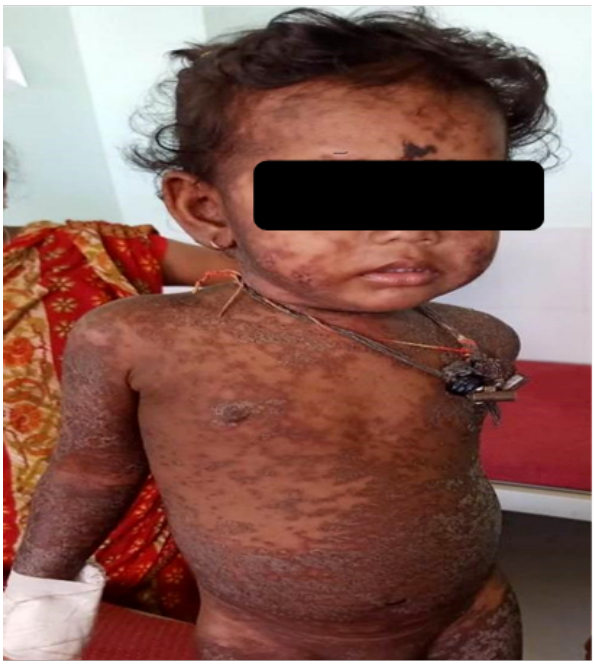

Figure 1: Amoxycillin /Clavulanic acid induced TEN in the youngest patient (2 years) in this study.

Clinical Patterns In Relation To Drugs

Stevens - Johnson syndrome (SJS)

In this study, anticonvulsants were mainly incriminated in SJS causing 45.45% of reactions. James J et al [23] -2005 reported similar results where anticonvulsants caused 42.86% of SJS. Among anticonvulsants, Carbamazepine caused maximum reactions (27.27%) in this study as in figure 2.

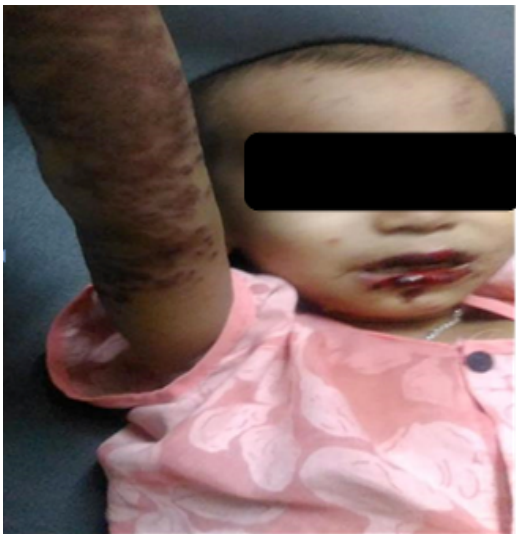

Figure 2: Carbamazepine induced SJS in a 3 year old female child.

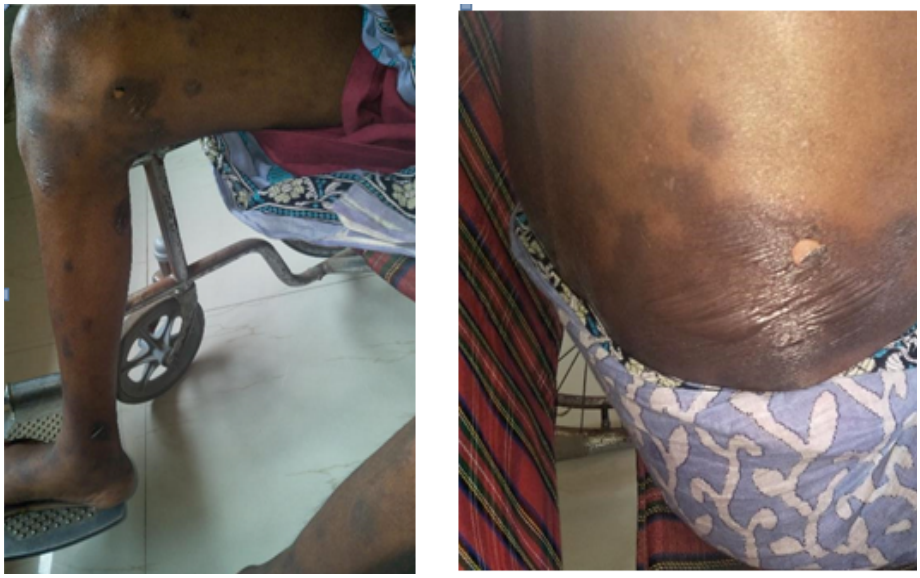

Figure 3: Nimesulide induced SJS-TEN overlap in a 42 year old female.

SJS – TEN Spectrum

In this study, 2 cases were found in the SJS-TEN spectrum. Carbamazepine was the culprit drug in 1 case and Nimesulide was found to be the culprit drug in 1 case (figure 3). Sharma R et al17-(2017) found two cases of SJS/TEN overlap, out of which one case was due to amoxycillin/clavulanic acid and one case was gardenal.

Toxic Epidermal Necrolysis (TEN)

In this study, anticonvulsants were the most common drugs implicated in 42.86% of TEN. Among them, carbamazepine and phenytoin caused 28.57% and 14.29% of TEN respectively. Sharma VK et al [24] -2001 reported anticonvulsants were responsible for 51.5% of TEN and phenytoin caused 24.24% of reactions. James J et al [23] -2005 found carbamazepine as causal drug for 50% of TEN.

Acute Generalized Exanthematous pustulosis

5 out of 6 cases (83.33%) of AGEP were due to antimicrobials. (Azithromycin in 2 cases, amoxycillin/clavulanic acid, terbinafine and ofloxacin each 1 case).

Paracetamol was causative in 1 case. Roujeau JC et al [25]-1991 reported in a series of 63 cases of AGEP, antibiotics were implicated in 80% of cases.

Misirlioglu D et al [21] -2017 reported antibiotics were implicated in 85.7 % of cases of AGEP.

Drug Rash with Eosinophilia and Systemic Symptoms: In this study, we found 5 cases of DRESS, Anticonvulsants were implicated in 40% of DRESS [Phenytoin in 1 case and carbamazepine in 1 case (figure 4)]. Antimicrobials were causative of 40% DRESS (dapsone in 1 case, amoxycillin/clavulanic acid in 1 case).

Sulfasalazine was the causal drug in 1 case of DRESS. Misirlioglu D et al [21] -2017 reported 50% of cases of DRESS due to Antibiotics and 37.5% cases of DRESS were due to Anticonvulsants.

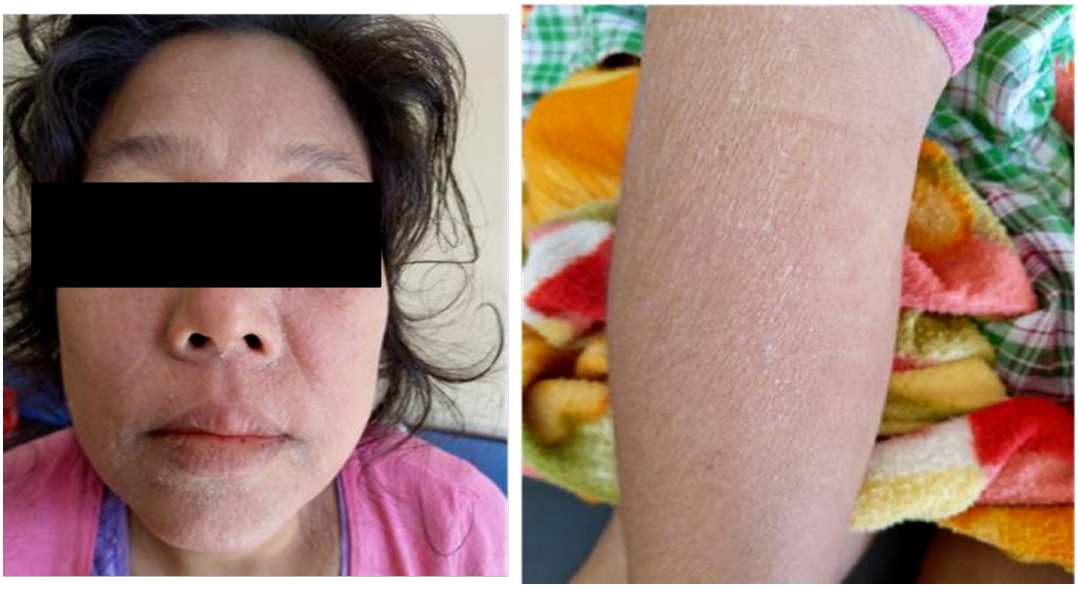

Figure 4: Carbamazepine induced DRESS

Table 1: Clinical (Morphological) Patterns of Severe Cutaneous Adverse Reactions (SCARs)

Clinical(Morphological) Patterns	Number Of Patients	Percentage (%)
Stevens-Johnson Syndrome (SJS)	11	35.48
SJS-TEN Overlap	2	6.45
Toxic Epidermal Necrolysis (TEN)	7	22.58
Acute Generalized Exanthematous Pustulosis (AGEP)	6	19.35
Drug Reaction With Eosinophilia And Systemic Symptoms	5	16.13
Total	**31**	**100.00**

Duration from Drug Administration to Cutaneous Reactions (Reaction Time)

The duration from the drug administration to cutaneous reactions (Reaction time) ranged from 12 hours to 60 days in this study. Shorter duration of 12 hours was seen in 1 case of TEN associated with re-exposure of the same drug Cotrimoxazole. Shorter duration of 12 hours was also seen in 2 cases of AGEP as shown in Table 2.

Loo CH et al [15] -2018 found range (3-29.4 days). Sashidharanpillai S et al [16] – 2015 reported a latent period of 12 hours to 90 days.

Table 2: Duration from Drug Administration to Cutaneous Reactions (Reaction Time)

Clinical Patterns	Reaction Time
Stevens-Johnson Syndrome	2 Weeks To 3 Weeks
Sjs/Ten	10 Days To 3 Weeks
Toxic Epidermal Necrolysis	12 Hours To 3 Weeks
Acute Generalized Exanthematous Pustulosis	12 Hours To 4 Days
Drug Rash With Eosinophilia And Systemic Symptoms	3 Weeks To 8 Weeks

Involvement of Skin and Mucosa

Skin, oral and conjunctival mucosa were involved in 6 (54.54%) patients of SJS, 1 (50%) patients of SJS/TEN overlap, 2 (28.57%) patients of TEN and 2 (40%) patients of DRESS. Skin, oral, conjunctival, nasal, anal and genital mucosa were involved in 1 (9.09%) patients of SJS and 2 (28.57%) patients of TEN.

Skin, oral and genital were involved in 4 (36.36%) patients of SJS, 1 (50%) patients of SJS/TEN

overlap and 3 (42.86%) patients of TEN. Nonfollicular superficial pustule was seen in 100% cases of AGEP. Maculopapular exanthema was seen in 60% of DRESS cases and urticarial exanthema in 40% DRESS cases. It is evident from the review that above mentioned conditions involves skin and various extent of mucosa (oral, conjunctival, genital, nasal and anal). Findings are depicted in Table 3. Misirlioglu D et al [21] -2017 reported cutaneous manifestations in 94.29% cases of SJS/TEN with oral plus conjunctival involvement in 68.57% cases, oral plus conjunctival plus genital mucosal involvement in 22.86% cases, oral plus genital mucosal involvement in 8.57% cases. He also reported 100% cutaneous involvement in DRESS with oral plus conjunctival mucosal involvement in 12.5% cases.

Routes of Drug Administration

In this study, most of the drug reactions occurred through oral route. 93.55% of drugs were administered through the oral route. Injectable caused only 6.45% of reactions.

Oral drugs significantly caused more drug reactions because oral formulations are prescribed more and preferred over injectable as it is easy to administer and cost effective.

Further, oral medications are easily available over the counter (OTC) and injections are given in strict precautions in hospital under supervision.

Table 3: Clinical Findings

Clinical Findings	SJS (11)	SJS/TEN(2)	TEN (7)	AGEP (6)	DRESS (5)
Maculopapularexanthema	-			-	**3(60%)**
Bullous lesions	5 (45.45%)	1 (50%)	3 (42.8%)	-	-
Epidermal detachment	11 (100%)	2(100%)	7 (100%)	-	
Target like lesion	11 (100%)	2(100%)	5 (71.43%)	-	-
Urticarial rash	-			-	2(40%)
Nonfollicular superficial pustules	-			6(100%)	-
(Oral+ conjunctival) Mucosa	6(54.54%)	1 (50%)	2 (28.57%)	-	2(40%)
(Oral + conjunctival + genital + nasal +anal) Mucosa	1 (9.09%)		2 (28.57%)	-	
(Oral + genital)Mucosa	4 (36.36%)	1 (50%)	3 (42.86%)	-	
Lymphadenopathy	1(9.09%)	1 (50%)	3 (42.86%)	2(33.33%)	5(100%)

Modes of Availability of Drugs (Way of Dispensed Medication)

In this study, the majority of drug reactions were found to be caused by prescribed drugs (70.97%). Non- prescribed or OTC drugs were responsible for 29.03% reactions. OTC drugs were taken commonly for fever, headache, joint pain, dysentery, tooth-ache, upper respiratory tract infection and incriminated in AGEP 2 (6.45%) cases, in SJS 5 (16.13%) and TEN 2 (6.45%). Saha A et al [26] -2012 and Hiware S et al [27]-2013 also found similar results of 88.7% and 89.1% of reactions caused by prescribed drugs respectively. This indicates that major proportions of SCARs are due to prescribed drugs by physicians and also indicate that more patients are taking medicines after visiting physicians and prompt detection of SCARs are possible as patients reporting it to treating physicians at earliest.

Results of Clinical Tests

Nikolsky's sign was positive in all patients of TEN, SJS-TEN overlap and 2 cases of SJS which is per se Pseudo-Nikolsky's sign. Here, the underlying mechanism is necrosis of epidermal cells and not acantholysis as in true Nikolsky's sign. (Sachdev D [28] -2003). Bulla spread sign could not be elicited as bullae are sub epidermal in cases of SJS and TEN. Diascopy showed blanching erythema in 3 cases of DRESS.

Laboratory Abnormalities

In this study, anaemia was found in 45.45% of patients of SJS, 50% patients of SJS/TEN spectrum, 42.86% patients of TEN, 33.33% patients of AGEP and 60% patients of DRESS. Misirlioglu D et al [21] -2017 reported anaemia in 11.4% of patients with SJS-TEN spectrum, 6.3% of DRESS. This disparity might be due to concomitant presence of diseases like malnutrition, hemoglobinopathies and chronic parasitic infestations, etc. which are quite common in this part of the country. Leukocytosis was observed in 18.18% of SJS, 100% of SJS/TEN overlap, 57.14% of TEN, 100% of AGEP and 40% of DRESS.

Ting HC and Adam BA [29] 1985 also reported similar results (24%) of their patients of SJS. Leukocytosis is seen in almost all cases of AGEP. [31] Leukopenia was observed in 14.29% cases of TEN. Misirlioglu D et al [21] -2017 also reported leukopenia in 11.4% of the SJS-TEN spectrum. In this study, atypical lymphocytes were present in 20% DRESS. Misirlioglu D et al [21] -2017 reported atypical lymphocytes in 25% DRESS. In this study, eosinophilia was observed in 54.55% of SJS, 28.57% of TEN and 100.00% of DRESS.

Misirlioglu D et al [21] -2017 reported eosinophilia in 100% of DRESS. Raised ESR was found in 54.55% SJS, 50% SJS-TEN overlap, 57.14% TEN, 66.66% AGEP and 60% DRESS.

Misirlioglu D et al [21] -2017 reported raised ESR in 62.9% of SJS-TEN spectrum, 56.3% of DRESS and 100% of AGEP. Hence, this finding is close to their observation. In this study, elevated Liver enzymes (SGOT, SGPT and ALP) were found in 72.73% SJS, 100% SJS-TEN overlap, 100% TEN and 100% DRESS. Sharma R et al [17] -2017 found liver function abnormalities in 60% of SJS, 100% SJS-TEN overlap, 100% of DRESS and 100% TEN patients which is similar to this study. Serum electrolyte imbalance (decreased serum Na+ and K+) were found in 100% SJS, 100% SJS-TEN overlap, 100.00% TEN and 60.00% DRESS. 16.67% of ED, 30% of SJS and 100% of TEN. Serum electrolyte imbalance could be due to barrier dysfunction of skin as a consequence of epidermal necrosis (SJS and TEN).

The involvement of oral mucosa further prevents oral intake which complicates the situation. Serum creatinine was found to be higher in 18.18% SJS, 50.00% SJS-TEN overlap, 28.57% TEN and 40% DRESS. Ting HC and Adam BA [29] -1985 reported almost similar findings (29%) in their patients with SJS. Increased fluid losses from both Trans epidermal water loss and the higher basal metabolic rate may result in dehydration and subsequently renal insufficiency.

Proteinuria found in 18.18% SJS, 50% SJS-TEN overlap, 28.57% TEN, 20% DRESS. Hematuria found in 18.18% SJS, 50% SJS- TEN overlap and in 71.43% TEN. Ting HC and Adam BA [29]-1985 found almost similar results in SJS- hematuria in 32% and proteinuria in 21%. Haematuria in some cases might be falsely positive due to the presence of erosion in the genital tract and thus blood traces.

Results of Special Test

Tzanck Test: Necrotic keratinocytes and leukocytes were found in 2 cases of TEN.

Pus Culture: In this study, Pus culture was done in pustular lesions of all 6 cases of AGEP. Results revealed no growth of any organism i.e. sterile. Pus culture and sensitivity was also done in SJS/TEN spectrum with epidermal detachment, out of which 6 cases of SJS, 1 case of SJS-TEN overlap, 5 cases of TEN came out to be positive for MRSA and Pseudomonas.

All of them were sensitive to Amikacin and Linezolid.

Results of Causality Assessment

For assessment of causality of SCARs, Naranjo algorithm[124] was followed and the following results were found- Definite 29.03%, Probable 67.74% and Possible 3.23%. Jha N et al [30] in 2018 found – Definite 30.62%, probable 69.38%, and possible 0%. Sharma R et al [17] in 2017 found – Definite 45.45%, probable 50%, and possible 4.5%.

Outcome and fate in patients of SCAR

In this study 81.82% SJS, 100% OF AGEP and DRESS recovered without sequelae. 18.18% SJS, 100% of SJS/TEN and 57.14% recovered with sequelae. Mortality was seen in 42.86% TEN. Choudhury MNG, et al in 2016 found recovery without sequelae in SJS as 78.2%, TEN 35.7% and DRESS 100%. Recovered with sequelae in SJS 8.7%, TEN 21.43% and DRESS 33.33%. Mortality in SJS 13.04, TEN 35.71%.

Advantages of this study

The study was a prospective study which collected information on the incidence, manifestation of Severe cutaneous adverse reaction in a large population base, included both inpatients and outpatients has been compiled in this study which was not done before. Though there are many reported studies on ACDR, there are very few studies on the severe forms i.e. SCAR and most of the studies on SCAR are retrospective analysis and chart reviews, which was not the case in this study.

Limitations of the study

1. Sample size in our study was small. Only 36 patients presented to our department during the study period.

2. Rechallenge could not be performed in this study as rechallenge in SCAR is considered to be unethical and it can be fatal.

Conclusion

Severe cutaneous adverse reactions are highly troublesome and fatal conditions and are to be treated as an acute emergency, preferably in a Dermatology ICU. A sound knowledge of different clinical patterns and common causative drugs may lead to early suspicion and recognition so that the offending drug can be recognized early and stopped as soon as possible to limit the morbidity and mortality.

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