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Original Research Article

A study of clinical spectrum of patterns of cutaneous adverse drug reactions in a tertiary care hospital

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ABSTRACT

Background: Adverse drug reactions are unwanted pharmacodynamic effects following administration of a drug. With an increase in number of newer drugs adverse drug reactions have become very common in recent times. Among them cutaneous reactions have been steadily gaining importance and constitute a major proportion of all the adverse drug reactions.
Methods: This observational study was conducted at Sri Siddhartha Medical College and Hospital Tumkur, Karnataka, India, involving 73 patients with cutaneous adverse drug reaction (CADR) during November 2016 to May 2018. The aim of the study is to identify the causal drug and categorised into definite/probable/possible Naranjo Algorithm scale was used.
Results: The mean age of study participants was 35 years. Majority of cases observed had fixed drug eruptions (FDE: 37%), followed by maculo papular drug reaction (MPDR: 26%). Antimicrobials (42%), non-steroidal anti-inflammatory drugs (NSAIDs: 26%), anticonvulsants (9.5%) were commonly implicated drugs causing CADR. Among those with FDE, definite causality was highest for NSAIDs (9.6%) predominantly paracetamol whereas in MPDR definite causality was noted with anti-tubercular drugs (rifampicin 1.4%) and probable causality was highest for cephalosporins (5.5%) predominantly cefpodoxime. In present study it was observed female patient aged ≥35 years showed statistically significant mucosal involvement and past history of CADRs.
Conclusions: A wide range of clinical spectrum of CADRs ranging from FDE to serious toxic epidermal necrolysis was observed. Most of these drug eruptions were caused by antimicrobials. Eliciting past history of CADRs with causal association will help to prevent and manage cases in a better way.

Keywords: CADR, Causal drug, Naranjo scoring

INTRODUCTION

Adverse drug reactions (ADR) can be defined as 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product. It has been estimated that ADRs represent the fourth to the sixth leading cause of death.[1,2] ADRs are often, an overlooked complication of drug therapies leading to morbidities.[3,4]

Cutaneous adverse drug reactions (CADRs) are probably the most frequent manifestations of all drug sensitivity. Different classes of drugs can produce a wide spectrum of cutaneous manifestations ranging from exanthematous rashes to toxic epidermal necrolysis (TEN). The reactions

include exanthematous eruption, pruritis, erythema multiforme, fixed drug eruption, exfoliative dermatitis (ED) and others. Some severe CADRs may result in serious morbidity and even death.[5-7] The exact incidence and prevalence of CADR are unknown, estimates between 2.0% to 2.4% have been reported worldwide. An incidence of 0.38% has been reported from India and antibiotics account for 7% of cases. Immunosuppressed patients are most frequently affected.[1] A hospital- based surveillance by the 'WHO International Programme for adverse reaction monitoring' identified skin as the most frequently affected organ in ADR. They account for 3-6% of all hospital admissions and 5-9% of hospital admission costs.[8] Therefore they are a big burden on the public healthcare system, especially in low income countries.

Effects of medicines vary grossly among populations of different countries and also various regions of the same country that can be attributed to the differences in prescribing practices, food habits, genetics, diseases, environmental variables and pharmaceutical manufacturing protocols. Hence with these variations and lack of data on CADRs, very few published studies have assessed the epidemiological and clinical features of drug reactions in India and still fewer in South India.[5-7,9]

With an increase in the number of newer drugs, ADR have become very common in recent times. Among them cutaneous reactions have been steadily gaining importance and constitute a major proportion of all the ADR. In order to detect and prevent the CADR we need a system called pharmacovigilance.

Aim

The aim of the present study is to determine the clinical spectrum of CADRs and to establish the causal relationship between the drug and CADRs using Naranjo scale.

METHODS

It was an observational study was conducted at Sri Siddhartha Medical College and Hospital Tumkur, Karnataka, India, over a period of one and a half years from November 2016 to May 2018 using purposive sampling method. The data has been collected by direct examination of the patient after approval from the institutional ethical committee after obtaining written informed consent from the patient. We included all age group patients of either sex with CADRs of skin and mucous membrane, associated with drugs, vaccines and blood products. Patients on other systems of medicine like Homeopathy and Ayurveda were excluded.

Patient included in the study was been thoroughly explained regarding nature and purpose of study. A detailed history pertaining to the demographic data, drug history, reaction time, previous allergic history, duration of reactions, type of cutaneous reactions, complications were noted. Cutaneous examination was done to determine the involvement, morphology, type of cutaneous eruption and mucosal involvement. If more than one drug was thought to be responsible the most likely offending agent was noted and the impression was confirmed by subsidence of rash withdrawal of the drug. To identify the causal drug, questionnaire has been asked according to Naranjo Algorithm.[10] The algorithm consists of 10 weighted questions that yield the following association between total score and causal relation. Obtained score helps in predicting causal association: 0 points=doubtful; 1–4 points=possible; 5–8 points=probable; and 9 or more points=definite.

RESULTS

Maximum number of cases were between the age group of 20–39 years (n=31, 42.5%). The youngest patient was 5 months old male and eldest patient was 75 year old male. Out of 73 cases, 29 patients had history of past reaction to drugs, in which males were 18 and females were 11 (Figure1).

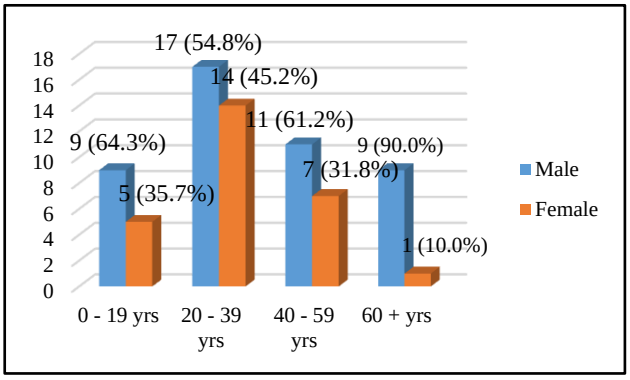

Figure 1: Age distributions of the study subjects according to gender.

The most common sites involved among both males and females were skin (58.7% and 55.6%) followed by mucosa (23.9% and 37.0%) and the combined skin and mucosal involvement (17.4% and 7.4%) respectively (Figure 2).

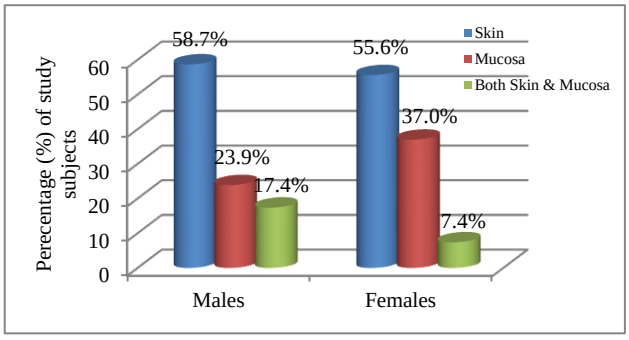

Figure 2: CADRs according to the sites involved and gender.

Majority i.e., 52.0% of those with fixed drug eruption (Figure 3) and 100.0% of those with angioedema had definite reactions. Majority i.e., 94.7% with maculo papular drug reaction (MPDR) (Figure 4), 100.0% with Drug induced urticaria (DIU) and Steven Johnsons syndrome (SJS) each (Figure 5), 66.7% of those with erythema multiformae (EM), 100.0% with drug induced acneform eruption (DIAE), drug reaction involving oral mucosa (DROM), drug hypersensitivity syndrome (DHS), post transfusion purpura (PTP) and TEN each had probable reactions (Figure 6). Equal proportions of those with ED had probable and definite reactions (Figure 7) (Tables 1 and 2).

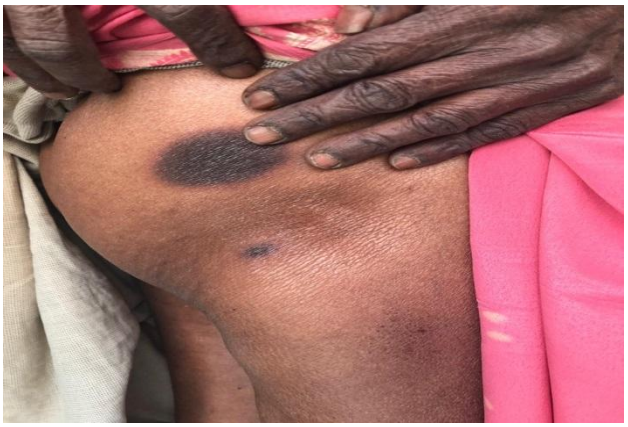

Figure 3: Fixed drug eruption to acelofenac in a female patient aged 65 years.

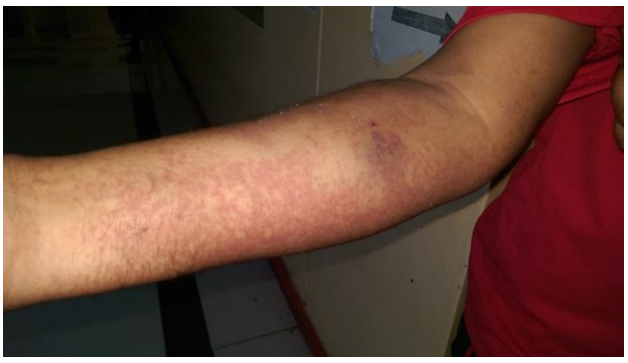

Figure 4: Maculo papular drug reaction to ceftriaxone in a male patient aged 27 years.

Figure 5: SJS caused by INH in a male patient aged 39 years.

Figure 6: TEN caused by ibuprofen in a male patient aged 1 year.

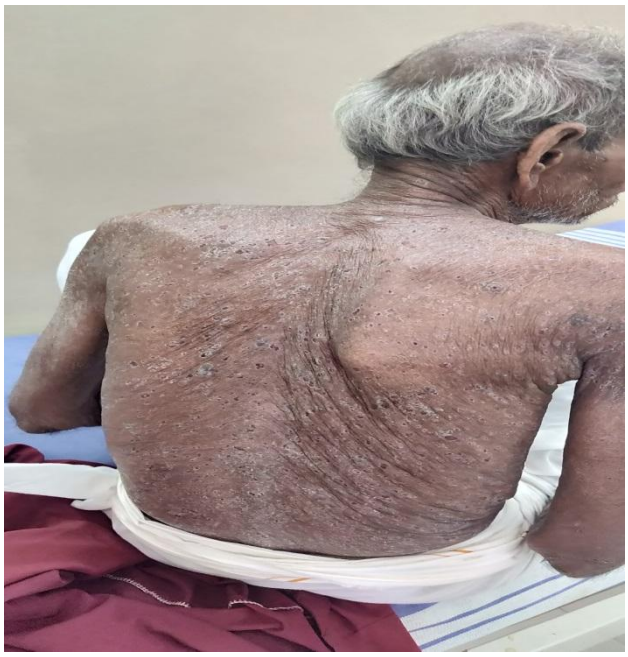

Figure 7: ED caused by ethambutol in a male patient aged 70 years.

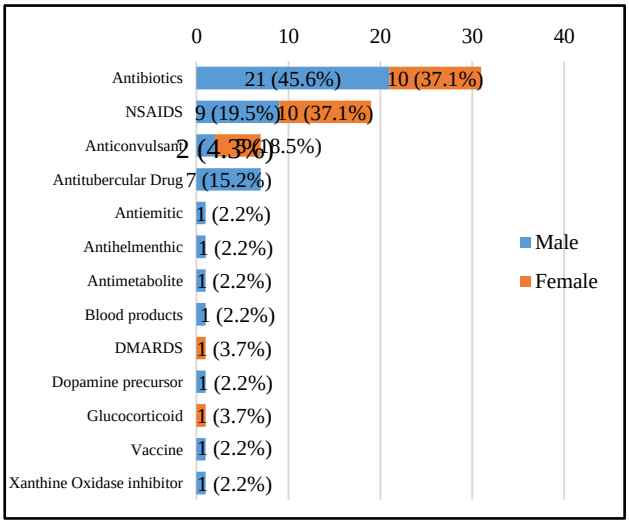

Figure 8: Drug categories producing CADR based on gender.

Table 1: Pattern of CADRs and Naranjo interpretation.

Pattern	Naranjo interpretation		Total
	Definite (≥9)	Probable (5-8)	
FDE	14 (51.9)	13 (48.1)	27 (100.0)
MPDR	01 (5.3)	18 (94.7)	19 (100.0)
DIU	00 (0.0)	9 (100.0)	9 (100.0)
SJS	00 (0.0)	05 (100.0)	5 (100.0)
EM	01 (33.3)	02 (66.7)	3 (100.0)
DIAE	00 (0.0)	02 (100.0)	2 (100.0)
ED	01 (50.0)	01 (50.0)	2 (100.0)
DIP	00 (0.0)	01 (100.0)	1 (100.0)
Angioedema	01(100.0)	00 (0.0)	1 (100.0)
DROM	00 (0.0)	01 (100.0)	1 (100.0)
DHS	00 (0.0)	01 (100.0)	1 (100.0)
PTP	00 (0.0)	01 (100.0)	1 (100.0)
TEN	00 (0.0)	01 (100.0)	1 (100.0)
Total	18 (24.6)	55 (75.4)	73 (100.0)

Table 2: Various factors associated with Naranjo interpretation.

Variables		Naranjo interpretation		χ^2 value (P value)
		Definite (≥9)	Probable (5-8)	
Age in years	<35	08 (21.6)	29 (78.4)	0.76; (0.38)
	≥35	11 (30.6)	25 (69.4)	
Gender	Males	11 (23.9)	35 (76.1)	0.04; (0.85)
	Females	07 (25.9)	20 (74.1)	
Sites	Skin	09 (21.4)	33 (78.6)	6.49; (0.039)*
	Mucosa	07 (33.3)	14 (66.7)	
	Both	02 (20.0)	08 (80.0)	
Past reported CADRs	Yes	17 (58.6)	12 (41.4)	(<0.01)*
	No	01 (2.3)	43 (97.7)	
Self-medication	Yes	06 (46.2)	07 (53.8)	1.93; (0.16)
	No	40 (66.7)	20 (33.3)	

*P value using chi square test showed significant association in site involved (0.039) and past reported cadre (<0.01) in study group.

DISCUSSION

CADRs are an important group of disorders which pose considerable amount of diagnostic and therapeutic challenges. Among all the drugs causing CADRs in this study, maximum number of cases were between the age group of 20–39 years (n=31, 42.5%) with mean age 35.18±19.16 years. The youngest patient was 5 months old male and eldest patient was 75 year old male, Similar to study by Dimri et al, noted that maximum number of CADRs were reported in the age group of 20-39 years (36.9%).[11]

The present study noted similar finding to Nivethitha et al, male preponderance (63.0%) and (77.0%) respectively.[11] However few studies also report female preponderance and that gender difference has been attributed to the consumption of multiple drugs and high number of elderly population in females.[13-15]

The most common sites involved among both males and females were skin (58.7% and 55.6%) followed by mucosa (23.9% and 37.0%) and the combined skin and mucosal involvement (17.4% and 7.4%) respectively. Similar to study noted by Sharma et al (Table 2).[16]

Forty percent gave positive history of previous CADRs similar to the study findings by Amrinder et al, (38.0%).[17] In a study conducted in urban Puducherry by Selvaraj et al, 12.0% of them practiced self-medication similar to the current study where it was noted to be 18.0%; however they noted a significant association between gender and self-medication (Table 2).[12]

Among those with CADR, proportion of females having self-medication practices was noted to be higher (26.0%) compared to males (13.0%). However there was no statistically significant association between self-medication practices and gender (p>0.05).

All drugs in a way are capable of producing any type of reaction in susceptible individuals however, some drugs are more likely to induce certain reaction patterns and this can also give a clue regarding the likely causative drug.

The most commonly observed morphological pattern according to Amrinder et al, was fixed drug eruptions (33.3%) followed by maculopapular rash (30.8%) and SJS (5.8%). Similarly in the current study, fixed drug eruptions (37.0%) followed by maculopapular rash (26.0%) were the most common except for SJS wherein the proportions were comparable to the current study (6.8%). However next in line was DIU reactions in the current study and this difference noted may be due to the varied type of drugs prescribed and their associated reactions (Table 1).[17]

Murray et al similar to our study findings, the most common suspected drug class causing CADRs were antimicrobials 24 cases (46.15%), followed by NSAIDs 17 cases (32.69%) and antiepileptics 9 cases (17.3%) wherein our study too, antimicrobials, NSAIDs and antiepileptics were commonly implicated drugs causing CADR among 42.0%, 26.0% and 9.5% respectively. Except for the few differences majority of our findings related to common suspected drug class causing CADRs were comparable with the study by Murray et al and such minor differences might be due to the different treatment brands and protocols practiced by the medical care providers in different study areas (Figure 8).[18]

In the current study antitubercular drugs (ATT) were noted to be causing drug induced acneiform eruptions similarly in a study by Junior and Kondo have mentioned ATT to be one of the causative drugs for drug induced acneiform eruptions.[20]

Saravu has mentioned that varying forms of skin reactions like maculopapular rash, erythema multiforme syndrome, acneiform eruptions, urticarial, lichenoid eruptions, and the more severe ED and SJS can occur with all ATT drugs.[21] In a case study reported by Ono et al have noted drug-induced hypersensitivity syndrome caused by carbamazepine similar to the current study findings wherein, a single case of drug hypersensitivity syndrome was caused by carbamazepine.[22]

Conti et al have mentioned in their study that PTP as a rare yet serious disease characterized by severe thrombocytopenia that occur after a blood transfusion and similarly in our study a single case of post transfusion purpura was caused by blood transfusion.[23]

There were isolated cases of CADRs with the use of Ondansetron, levamisole, methotrexate, blood transfusion, penicillamine, levodopa, betamethasone, DPT vaccine and allopurinol.

ADR are a major cause of morbidity, hospital admission, and even death. Hence it is essential to recognize ADRs and to establish a causal relationship between the drug and the adverse event. It is desirable that ADRs should be objectively assessed and presented based on an acceptable 'probability scale.' The causality assessment system proposed by the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre, and the Naranjo Probability scale are the generally accepted and most widely used methods for causality assessment in clinical practice as they offer a simple methodology. Among the various scales to find the association between the drug and the reaction, Naranjo scale was used results were 55 i.e., 75.0% reactions had probable associations and 18 i.e., 25.0% had definite association.

Among association between pattern of reactions and Naranjo interpretation. Majority i.e., 52.0% of those with fixed drug eruptions and 100.0% of those with angioedema had definite reactions. Majority i.e., 94.7% with MPDR, 100.0% with DIU and SJS each, 66.7% of those with EM, 100.0% with DIAE, DROM, DHS, PTP and TEN each had probable reactions. Equal proportions of those with ED had probable and definite reactions.

Shah et al had mentioned in their study that an ADR may require intervention including the stoppage of the suspected drug (s) and even hospitalization in severe cases. They also found that 14% of total and 16% of serious ADRs could have been prevented indicating requirement of hospitalization at least among 14% however the number of severe cases requiring hospitalization is not been mentioned and in our study majority i.e., nearly 59.0% cases required hospitalization and this may be due to the fact that the study being conducted in a tertiary care setting can project many a times a spurious association as most cases referred to tertiary centres will be serious cases that might need hospitalization.[24] All the reactions observed were recorded and reported to pharmacovigilance center of college.

CONCLUSION

With the causalities established, our study suggests and recommends an immense need for reporting the CADR. Identifying the risks, formulating the risk profile of various drugs and its administration, designing an appropriate pharmacovigilance plan to mitigate such risks and to explore the missing critical information which did not emerge during premarket phase-I/II/III trials may help in the safety precautions that need to be taken before prescribing any drugs.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Breathnach SM. Drug reactions. In: Burns T, Breathnach S, Cox N, Griffiths C, eds. Rook's textbook of dermatology. 8th ed. Blackwell Publishing; 2010: 75.1-77.
2. Klassen CD. Principles of toxicology and treatment of poisoning. In: Hardman GJ, Limbird LE, eds. Goodman's and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. Mc-Graw Hill; 1996: 63-75.
3. Mahatme N, Narasimharao R. A study of clinical patterns and causative agents of adverse cutaneous drug reactions. Indian J Drugs Dermatol. 2016;2:13-8.
4. Garg HK, John JL, Thomas IN, Muttappallymyalil J, Kadam W, Sreedharan J. Spectrum of cutaneous adverse drug reactions in a tertiary health care centre in Ajman, UAE. Gulf Med J. 2015;4(1):2-7.
5. Dimri D, Raina RS, Thapliyal S, Thawani V. Retrospective analysis of pattern of cutaneous adverse drug reactions in tertiary hospital of Pauri Garhwal. J Clin Diagnos Res. 2016;10(5):FC01-6.
6. Sushma M, Noel MV, Ritika MC, James J, Guido S. Cutaneous adverse reactions: a 9-year study from a South Indian hospital. Pharmacoepidemiol Drug Saf. 2005;14(8):567–70.
7. Mahatme N, Narasimharao R. A study of clinical patterns and causative agents of adverse cutaneous drug reactions. Indian J Drugs Dermatol. 2016;2:13-8.
8. Borroni RG. Pharmacogenetic markers of severe cutaneous adverse drug reactions. G Ital Dermatol E Venereol Organo Uff Soc Ital Dermatol E Sifilogr. 2014;149(2):219–26.
9. Sharma VK, Sethuraman GG. Adverse cutaneous reactions to drugs: an overview. J Postgrad Med. 1996;42:15-22.
10. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-45.
11. Simons FER. Anaphylaxis. J Allergy Clin Immunol. 2008;121:S402-7.
12. Nivethitha T, Manickavasagam S, Balasubramanian N, Thaejesvi GS. A study of cutaneous adverse drug reactions in a tertiary care teaching hospital. IOSR J Pharm. 2017;7(4):18-22.
13. Naldi L, Conforti A, Venegoni M, Troncon MG, Caputi A, Ghiotto E, et al. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. Br J Clin Pharmacol. 1999;48:839-46.
14. Akpinar F, Dervis E. Drug eruptions: An 8-year study including 106 inpatients at a dermatology clinic in Turkey. Indian J Dermatol. 2012;57:194-8.
15. Patel TK, Thakkar SH, Sharma DC. Cutaneous adverse drug reactions in Indian population: A systematic review. Indian Dermatol Online J. 2014;5(S2):76-86.
16. Sharma R, Dogra N, Dogra D. A clinical study of severe cutaneous adverse drug reactions and role of corticosteroids in their management. Indian J Drugs Dermatol. 2017;3:20-3.
17. Amrinder R, Kaur I, Singh J, Kaur T. Monitoring of cutaneous adverse drug reactions in a tertiary care hospital. J Pharmacovigilance. 2016;4:207.
18. Selvaraj K, Ramalingam A. Prevalence of self-medication practices and its associated factors in Urban Puducherry, India. Perspect Clin Res. 2014;5:32-6.
19. Murray JL, Vedavathi H, Prasad NS, Dadapeer HJ, Revankar SP. A study on cutaneous adverse drug reactions at district Mc. Gann teaching hospital, Shimoga institute of medical sciences, Shivamogga, Karnataka, India. Int J Basic Clin Pharmacol 2016;5:1343-8.
20. Pontello Junior R, Kondo RN. Drug-induced acne and rose pearl: similarities. Anais Brasileiros De Dermatologia. 2013;88(6):1039-40.
21. Saravu K. Adverse Drug events With anti-tuberculosis therapy: what every GP should know. GP Clinics. 2016;6(12):12-7.
22. Ono Y, Shimo T, Shirafuji Y, Hamada T, Masui M, Obata K, et al. Drug-induced hypersensitivity syndrome caused by carbamazepine used for the treatment of trigeminal neuralgia. Case Reports Dent. 2016;2016:4605231.
23. Yokoyama AP, Dezan MR, Costa TH, Aravechia MG, Mota MA, Kutner JM. Diagnosis and management of post-transfusion purpura-case report. Blood. 2013;122(21):4834.
24. Shah SP, Desai MK, Dikshit RK. Analysis of cutaneous adverse drug reactions at a tertiary care hospital–a prospective study. Trop J Pharm Res. 2011;10(4):517-22.

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