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A Clinical Study Of Cutaneous Adverse Drug Reactions In A Tertiary Center

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Abstract: ***Background****: An adverse cutaneous reaction caused by a drug is any undesirable change in the structure or function of the skin, its appendages, or mucous membranes, and it encompasses all adverse events related to drug eruption, regardless of the etiology.*
Aim*: To study the prevalence and various clinical presentations of CADR among patients attending the DVL outpatient department (OPD) in a tertiary care hospital.*
Methods: *75 patients with adverse cutaneous drug reactions were included who came to Dept. of Dermatology, Venereology and Leprosy at Government General Hospital, Kurnool Medical College, Kurnool from November 2018 to November 2019. A thorough history was taken, and detailed clinical examination with all routine hematological and biochemical investigations and septic screening were done. The morphology of skin lesions was noted. The offending drug was withdrawn in the patients and appropriate treatment and counselingwere given.*
Results: *Male to female ratio was 1.2:1, with the most common age group being 21-30 years (28%). FDEwas the most common clinical type of drug reaction (28%) followed by SJS/TEN(13.3%), maculopapular rash(12%) and Urticaria(9.3%). SJS/TEN, Exfoliative dermatitis, DRESS were life-threatening and represented the severe variants of CADR(21.3%) in the study population. NSAIDs were the most common offending drugs (28%).Out of 75 patients, 6 (8%) were HIV reactive. Oral mucosa was involved in 20(26.66%) of the cases. In the present study, 2 cases of SJS/TEN proved to be fatal, while the outcome was satisfactory in the remaining cases.*
Conclusion:
Self-administering medicines/drugs prescribed by unqualified practitioners are the major causes of CADRs. The majority of CADRs are benign except for SJS-TEN/DRESS. Identification of the offending agent and prompt withdrawal of such drugs will result in the improvement of many cases
Keywords: *Cutaneous adverse drug reactions, FDE, NSAIDs*

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I. Introduction

Everyday a new drug enters the market leading tothe addition of many drugs to the physician's armamentarium. The extensive and indiscriminate use of drugs has led to increased incidence and a variety of modes of presentation of drug reactions. World Health Organization (WHO)[1] defines an adverse drug reaction (ADR) as "a response to a drug that is noxious and unintended and occurs at doses,[2]used in man for prophylaxis, diagnosis, or therapy of a disease or modification of physiological function." An adverse cutaneous reaction caused by a drug is any undesirable change in the structure or function of the skin, its appendages, or mucous membranes, and it encompasses all adverse events related to drug eruption, regardless of the etiology[3]. Because of the visible eruptions facilitating early and easy diagnosis, CADRs are the most frequently reported adverse reactions to drugs.

These reactions may vary from a trivial urticarial rash to life-threatening conditions like Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis; though rare[4,5], these can cause significant morbidity and mortality to the patient[6].

The overall incidence of adverse cutaneous drug reactions in developed countries is 1-3%, while the incidence in developing countries is thought to be higher between 2% and 5%.[7] However, the true incidence of cutaneous drug eruptions is challenging to determine, mainly because many patients with mild and transitory reactions do not come for reporting. On the other hand, cutaneous changes due to other etiology (e.g., viral exanthem misdiagnosed as morbilliform eruption and herpes labialis as bullous fixed drug reaction) are sometimes incorrectly attributed to drugs.

A diagnostic challenge arises when the patient takes multiple medications before drug eruption. The objective of the present study is to ascertain the clinicodemographic profile of suspected CADRs and the drugs causing CADRs and to find out the risk factors, if any, in a tertiary care center.

II. Methods

The present study is a prospective, open, observational study carried out in the Department of Dermatology, Venereology, and Leprosy at Kurnool Medical College & Government General Hospital, Kurnool, during a period of 1 year from November 2018 to November 2019. All patients attending the DVL OPD with active lesions of cutaneous adverse drug reactions due to systemic drugs were included in the study. A thorough clinical history of all the patients was taken and recorded according to preformed proforma. The precise history of drug intake, including allopathic, homeopathic, ayurvedic medicines, along with its temporal correlation with the initiation of the symptoms, was elicited with an emphasis on whether it was prescribed by a registered medical practitioner or self-administered. Detailed history regarding relevant dermatological or systemic diseases, atopy, past and family history of drug eruption was taken. Excluded were subjects who complained of only symptoms (e.g., itching) without visible skin lesions, those who could not recall the name of the suspect medicines consumed, and those whose lesions turned out to be other disease-related (e.g., viral exanthems, rash due to rickettsial infections, and collagen vascular diseases) on closer examination. A few subjects who reported to have consumed indigenous (ayurvedic and homeopathic) medicines were also excluded as the herbalingredients could not be identified in their case. The final diagnosis of CADR was made after excluding other possible causes having a similar clinical picture. Morphology of the presenting eruption, duration of the cutaneous rash, associated mucosal and systemic involvement and improvement on drug withdrawal were established. Rechallenge was not attempted in any of the patients. In case of more than one drug suspected, the most likely offending drug was noted and the diagnosis was confirmed by subsidence of the rash on withdrawing the drug. All routine investigations, including CBC, Complete urine examination, renal function tests, liver function tests, serum protein and blood sugar, septic screening, were done in all patients. In cases with SJS-TEN, the SCORTEN was calculated to assess the risk of mortality.
HIV-I and II testing was done in cases of severe CADRs and those cases with risk factors. The CD4 count was done in all HIV reactive patients.

Appropriate specific treatment was given to each patient. All patients were counselled and educated to avoid self-administration of the offending drugs. Each patient was given a list of drugs to be avoided in the future.

III. Results

A total of 75 patients of Cutaneous Adverse Drug Reactions were studied. In our study, the male to female ratio was 1.2:1, with the most common age group being 21-30 years (28%).The drug was prescribed by a registered medical practitioner in 21 cases (28%), by an unregistered medical practitioner(quack) in 45 patients(60%), while self-administered in 9 cases (12%). A most common route of admission was found to be oral (94.6%).The time interval between the intake of drug and onset of clinical features varied from 1 day to 2 years in the present study.Drugs used for fever, myalgias and arthralgias accounted for the majority of the cases, followed by URTI, GI problems, neurological problems etc., History of some cutaneous drug reaction in the past was present in 18 patients (24%).Lesions were generalized in 57 cases (76%) and localized in 18 cases (24%). In the present study, a Fixed drug eruption was the most common clinical type of drug reaction (28%) followed by SJS/TEN(13.3%), maculopapular rash(12%) and Urticaria(9.3%). Others were EMF,DRESS, Exfoliative dermatitis, AGEP, Acneiform eruptions, alopecia, hirsutism, erythema nodosum etc.,Of these, cases of SJS/TEN, Exfoliative dermatitis, DRESS were life-threatening and represented the severe variants of CADR(21.3%) in the study population. Among the offending drugs for CADRs, NSAIDs were the most common group (28%).The most common drugs causing FDE were a fixed-dose combination of Fluoroquinolone with Nitroimidazole followed by NSAIDs. Out of 75 patients, 6 (8%) were HIV reactive, and SJS/TEN was seen in 2 cases, FDE in 2 cases, maculopapular rash in 2 cases.Oral mucosa was involved in 20(26.66%) of the cases, while ocular and genital mucosa was involved in 8 (10.7%) and 14 (18.7%) cases, respectively. In the present study, 2 cases of SJS/TEN proved to be fatal, while the outcome was satisfactory in the remaining cases.

Table 1 :- Age And Sex Wise Distribution

AGE	MALE	FEMALE	TOTAL PATIENTS	PERCENTAGE(%)
0-10	3	0	3	4%
11-20	6	5	11	14.7%
21-30	11	10	21	28%
31-40	11	7	18	24%
41-50	7	6	13	17.3%
51-60	3	5	8	10.7%
61-70	1	0	1	0.01%
TOTAL	42	33	75	

Table 2:- Clinical Presentation Of Cutaneous Adverse Drug Reactions

SL.NO	PATTERN OF REACTION	NO.OF CASES	% OF CASES
1	FDE	21	28%
2	Maculopapular rash	9	12%
3	SJS/TEN	10	13.3%
4	Urticaria	7	9.3%
5	EMF	4	5.3%
6	DRESS	3	4%
7	Exfoliative Dermatitis	3	4%
8	Acneiform eruptions	4	5.3%
9	Alopecia	3	4%
10	AGEP	1	1.3%
11	Erythema nodosum	1	1.3%
12	Hirsutism	2	2.6%
13	Hyperpigmentation	2	2.6%
14	Ichthyosis on upper and lower limbs	1	1.3%
15	Lichenoid eruptions	3	4%
16	P.Rosea	1	1.3%

Table 3:- Suspected Drugs Causing Cutaneous Adverse Drug Reactions

SL.NO	OFFENDING DRUG	NO. OF CASES	% OF CASES
1	NSAIDS	21	28%
2	FQ/FQ+NITROIMIDAZOLE	8	10.7%
3	PENCILLINS	8	10.7%
4	ANTIEPILECTICS	7	9.3%
5	ATT	6	8%
6	CORTICOSTEROIDS	5	6.7%
7	DAPSONE	4	5.3%
8	NITROIMIDAZOLE	4	5.3%
9	ARV	3	4%
10	TETRACYCLINES	2	2.6%
11	ANTIMALARIALS	1	1.3%
12	CHEMOTHERAPY	1	1.3%
13	CICLOSPORINE	1	1.3%
14	CLOFAZIMINE	1	1.3%
15	DIURETICS	1	1.3%
16	QUINOLONES	1	1.3%
17	VACCINATION	1	1.3%

Table 4:- Time Relationship Of Cutaneous Adverse Drug Reactions

DURATION	ADVERSE DRUG REACTION
<24HRS	Maculopapular rash
Upto 1 week	FDE, Urticaria
1 week to 4 weeks	EMF, SJS, TEN, P.Rosea
1 month to 3 months	DRESS, Alopecia, Acneiform eruptions, AGEP
3 months to 6 months	Skin hyperpigmentation, Hirsutism, Alopecia
6 months to 1 year	Ichthyosis of upper and lower limbs

Table 5:- Mucosal Involvement

MUCOSA	NO. OF CASES	% OF CASES
Oral	20	26.7%
Ocular	8	10.7%
Genital	14	18.7%

Table 6:- Comparision Of Cadr Of This Study To Other Studies

CADR	Tejashviniet al[8]	Shah R et al[9]	PRESENT STUDY
FDE	13.3%	20%	28%
Maculopapular rash	16.6%	42.6%	12%
Urticaria	1.1%	12%	9.3%
SJS/TEN	16%	10.7%	13.3%
DRESS	15.5%	1.3%	4%
EMF	12.2%	6%	5.3%

IV. Discussion

Cutaneous adverse drug reactions cause severe distress both to thepatient and physician. They cause severe morbidity and mortality, especially in severe CADR[10]. It can also lead to discontinuation of the treatment of underlying conditions that compound the suffering of the patient[11]. Every dermatologist should have a comprehensive understanding of the spectrum of manifestations of varied presentations of CADR and also of the drugs which are responsible for such CADR.

The age range of our study was 3-65 years showing that no age is exempt from CADR. This is similar to other studies[8,9]. The majority(28%) of the patients belonged to the age group of 21-30 years which is identical to the study done by Pudukadan et al[12]., but in the study done by Tejashwini et al.[8], the majority of the patients belonged to 31-40 years. In our study,the male to female ratio was 1.2:1 which is similar to study done by Sharma et al[6]. our study result differs from the study done by Pudukadan[12] which showed slight female predominance.

CADR was more commonly found to be caused by prescription drugs than over the counter drugs in our study. A similar finding was noted in many other previous studies[9,13]. In this study,Fixed drug eruption was the commonest reaction encountered. This is followed by a morbilliform or maculopapular eruption and severe CADR(SJS/TEN/SJS-TEN overlap syndromes). This is similar to the study done by Pudukadan et al[12]., however, this is in contrast to the studies done by Tejashwini et al.[8], and Sharma et al[14]., where morbilliform or maculopapular eruption was the most common reaction pattern. Fixed drug eruption was most commonly caused by NSAIDs, followed by FDC of fluoroquinolones with a nitroimidazole. This is similar to the study done by Abanti et al[15]. NSAID group of drugs were the most common culprit drugs in our study which is similar to the studies done by Marfatia et al[13]., and Tejashwini et al[8]. Antimicrobial drugs were the most common culprit medications in the studies done by Sharma VK et al[14]. and Pudukadan et al[12]. A previous history of some cutaneous drug reaction was seen in 18 cases(24%), which is slightly less compared to the study done by Shah R et al[9]. (31.1%). Diclofenac(23%) was the most common individual drug followed in our study as opposed to Cotrimoxazole in Pudukadan et al[12]., and Carbamazepine in Tejashwini et al[8]. The most common indications for the intake of the culprit medications include fever, epilepsy, GI illness, URTI.

SJS-TEN was seen in 10 patients(13.3%), of which two are HIV positive. The drugs responsible for SJS-TEN in the present study were antiepileptics, NSAIDS, and FDC of fluoroquinolones and nitroimidazole. The majority of the patients had a satisfactory outcome, and 2 cases proved to be fatal, one due to hypovolemic shock and others due to aspiration pneumonia.

DRESS was seen in 3 cases in our study. Antiepileptics caused two cases, and Dapsone caused one. This was similar to the study done by Shah R et al[9]., where antiepileptics were the most common drugs causing DRESS.

The reaction time for various CADRs like FDE, maculopapular rash, urticaria, SJS-TEN was shorter, i.e., in the range of 1 day to 4 weeks; and it was longer for reactions like DRESS, exfoliative dermatitis, hirsutism, alopecia, etc., this was similar to the studies done by Sharma et al. and Abanti et al[15].

Among the HIV reactive patients, the morbilliform rash was seen due to Nevirapine. 2 cases had SJS-TEN.

The majority of the CADRs encountered in our study were benign with satisfactory recovery. Mortality has occurred only in cases with SJS-TEN. This is similar to that observed in Abanti et al[15]. Early identification and prompt diagnosis and initiation of early and accurate treatment can reduce morbidity and mortality. Education of the patients to be wary of the incriminating drugs of the CADR and avoiding them in the future is a crucial step in the management.

Polypharmacy has been observed in the present study. It is crucial to correctly identify the culprit medication so as not to unnecessarily avoid the medicines which do have a causal role in CADR.

V. Limitations

It is difficult to assess the exact culprit medication in polypharmacy cases as rechallenge cannot be done due to ethical reasons.

The exact incidence of CADR cannot be ascertained as it is a spontaneous ADR reporting. Many cases will be missed due to underreporting and self-limiting circumstances.

Long term followup and monitoring could not be done in many cases.

VI. Conclusion

The majority of CADRs are benign except for SJS-TEN/DRESS. NSAIDs, antibiotics, ATT drugs, and antiepileptics are the most common offending drugs. Hence thorough history taking to identify the culprit drug and prompt referral to the appropriate centerfor early management is essential for the prevention of morbidity and mortality due to drug reactions.

Self-administering medicines/drugs prescribed by unqualified practitioners are the major causes of CADRs. Polyprescription, particularly in elderly patients, is a major reason for CADRs and needs special attention to reduce the number of drugs whenever possible.

In many cases, identification of the offending agent and prompt withdrawal of such drugs will result in the improvement of many cases.

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Conflict Of Interest: none

Clinical Figures

Fig 1:- BULLOUS EMF

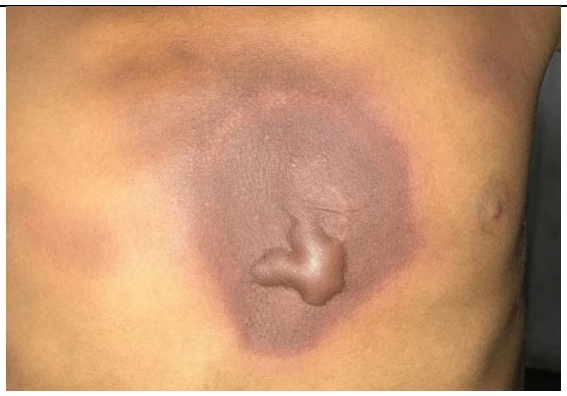
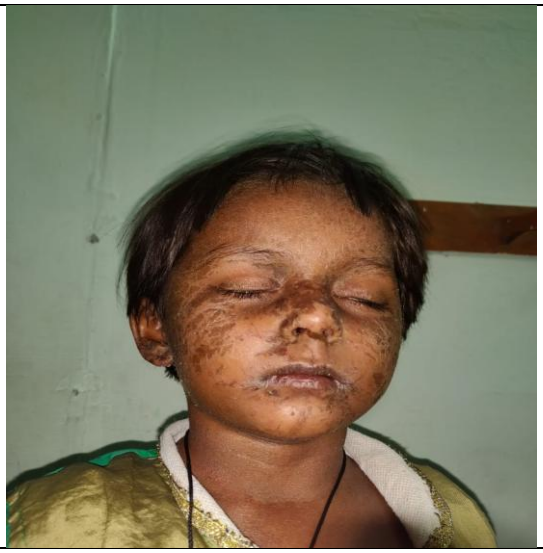


Fig 2:- BULLOUS FDE



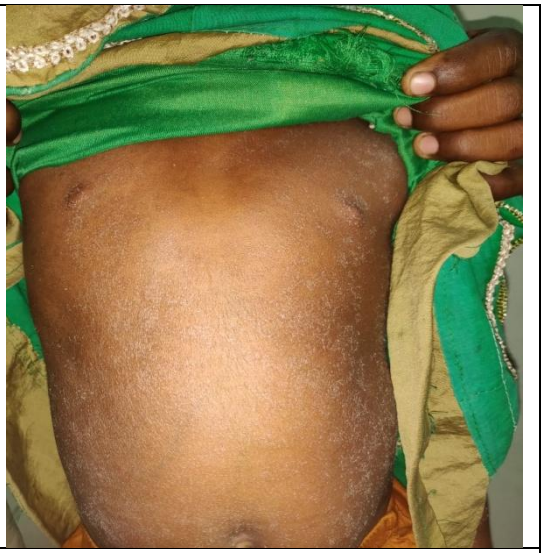


Fig 3,4:- DRESS SYNDROME

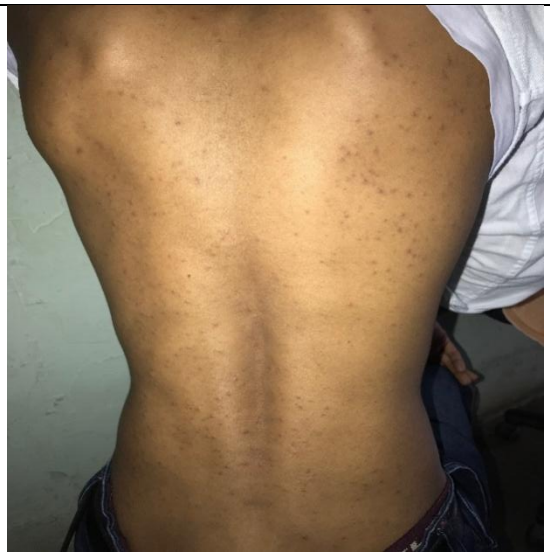


Fig 5:- ATT induced truncal acne

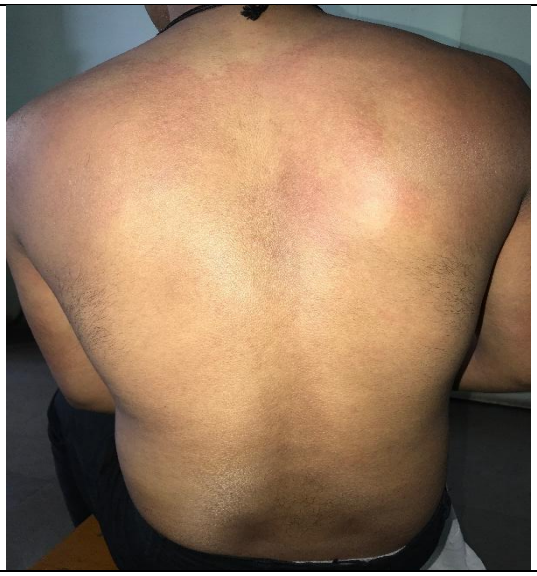
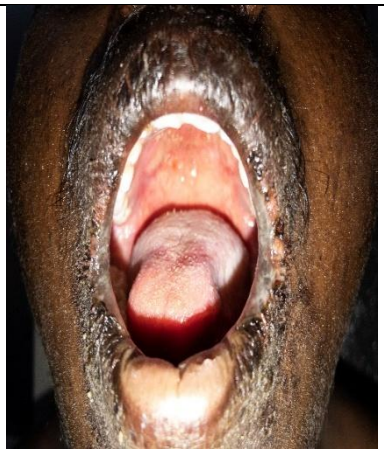
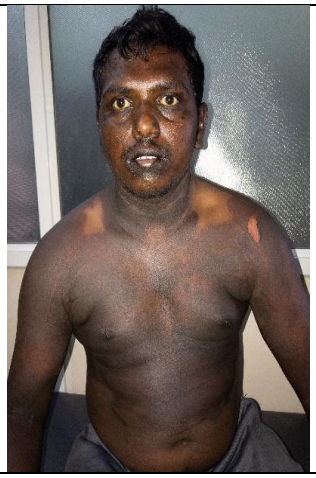


Fig 6:- NSAIDS induced Urticaria





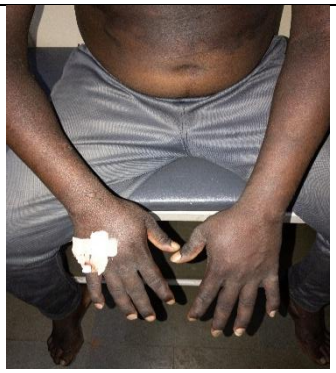


Fig 7,8,9 :- SJS-TEN

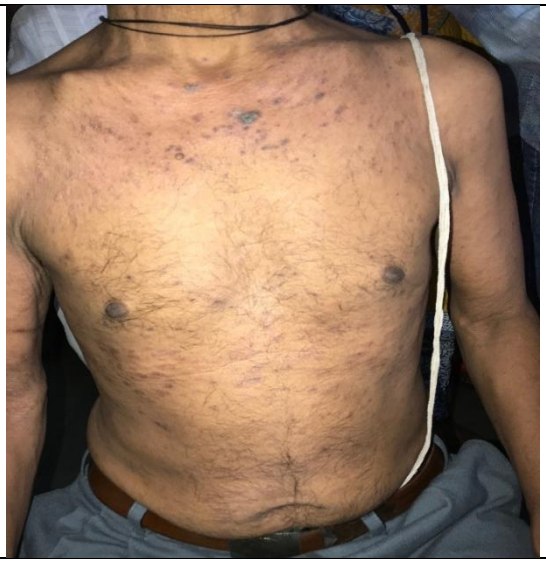


Fig 10:- ATT induced Lichen Planus

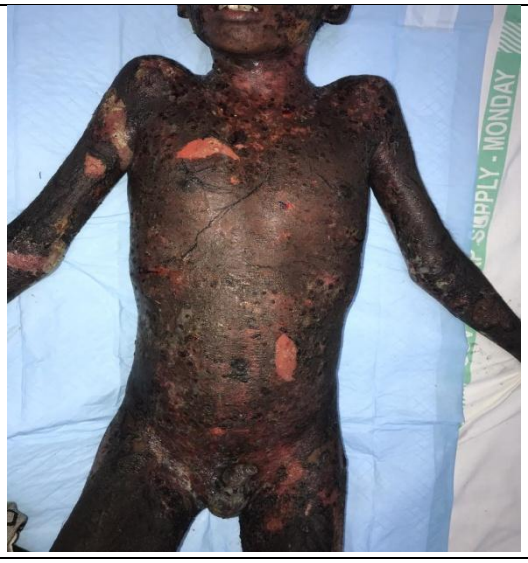
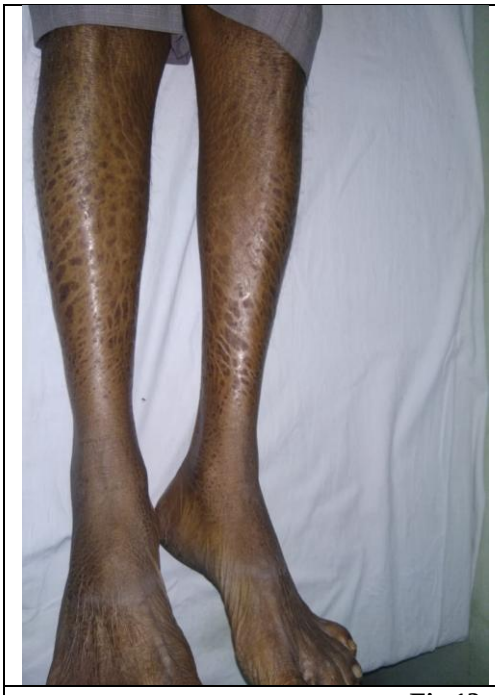


Fig 11:- TEN



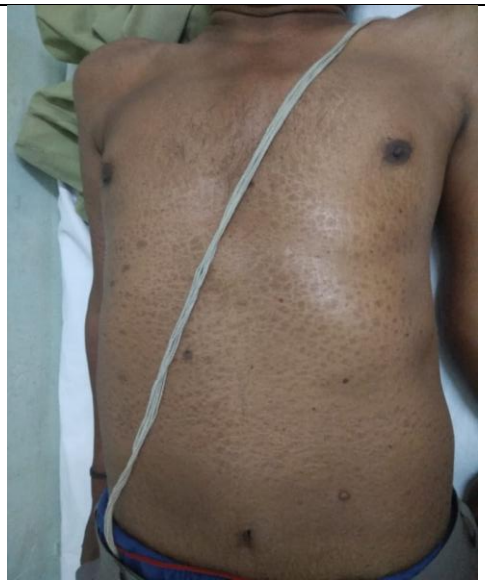


Fig 12:- ATT induced Icthyosis

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