CUTANEOUS ADVERSE DRUG REACTIONS

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DEFINITION

- CADR – defined as an unwanted or unintended drug reaction that causes any undesirable change in the structure or function of the skin, its appendages, or mucus membranes that occurs even at a normal dosage used for prophylaxis or treatment of disease.

- Can be solely limited to the skin, or may be a part of a systemic reaction.

- Ayurvedic, herbal and homeopathic products often considered Natural & Non-toxic can also cause drug reactions.

- A particular drug can cause different types of CADRs although some drugs are more likely to cause a particular drug reaction.
- Incidence of CADRs is 2 to 3 %
- Most common is Morbilliform rash (91%) followed by urticaria.
- Drug reaction can occur within few hours up to 6 weeks of drug intake.
- They account for significant morbidity & mortality
- A thorough & detailed history, good clinical examination is crucial & essential in establishing a diagnosis in possible CADRs.

CLASSIFICATION

- In 1977 and 81, Rawlins & Thompson proposed a sub-classification of ADR as Type A & B
- Still it is widely used today for an initial approach to ADR.
- The strength of this classification is its simplicity.

Type A reactions	Type B reactions
Nearly all individuals	15% of all ADR
Due to pharmacological activity of the drug	Not dependent on the pharmocological activity
Influenced by drug pharma-cokinetics , comorbidities & / or drug - drug interactions	-
Overdosing & drug binding to – target receptors are important	-
Dose dependent	Not dose dependent
Predictable	Not predictable (idiosyncratic)
Eg: Dry mouth - antihistamines	Eg: Drug allergy / drug hypersensitivity

- Type B reactions remain less clear and are essentially classified as “Non- A” type.

- Majority of Type B reactions involve the immune system and are drug hypersensitivity reactions.

- Not all ADRs fit in to these 2 categories, so, additional categories have been developed.

- These include

- Type C (continuing) – persist for relatively longer time
- Type D (delayed) - apparent after sometime
- Type E (end of use) – withdrawal reaction after stopping drug. Ex. anxiety, insomnia after stopping benzodiazepines

Pathophysiology mechanisms

- T cells play an important role in drug induced skin disease.

- 3 major pathogenic mechanisms described:

1. The allergic/immune stimulation : Hapten & prohapten concept.
2. Pharmacological stimulation of immune recepors : p-i concept
3. Alteration of the MHC-presented self-peptide

Hapten & prohapten concept

- This mechanism is the classical explanation for DHR and represents a true drug allergy.
- Drugs causing ADRs are small molecules called haptens which are non immunogenic by themselves.
- They are made immunogenic by binding to larger molecules.
- This covalent complex between drug and peptide is recognised by the T cells through APCs

- Memory cells are generated in the tissue which later produce drug reactions.

- Pencillins, cephalosporins, SMX-NO are known haptens- may cause exanthematous/ bullous rash/ other patterns .

P-I CONCEPT (PHARMACOLOGICAL STIMULATION OF IMMUNE RECEPTORS)

- This concept supports the theory that a drug is able to stimulate T cells directly without forming a hapten in a HLA dependent manner.

- In this model, offending drug binds to either the TCR or MHC protein I peptide independent manner to directly activate T cells.

- Occurs only in some individuals, and persons at risk can be identified, carrying the allele.
- Induction of a strong T-cell reaction is a characteristic feature of p-i stimulations.
- P-I reactions are involved in maculopapular eruptions, acute generalised exanthematous pustulosis, drug-induced liver injury, SJS-TEN & DRESS.

Alteration of MHC-presented self-peptide repetoire

- Reported with Abacavir.
- Drug binds to the antigen binding cleft of the MHC and alters the binding cleft and antigen specifcity of MHC.
- This results in presentation of novel peptides to the TCR and activation of the immune system.

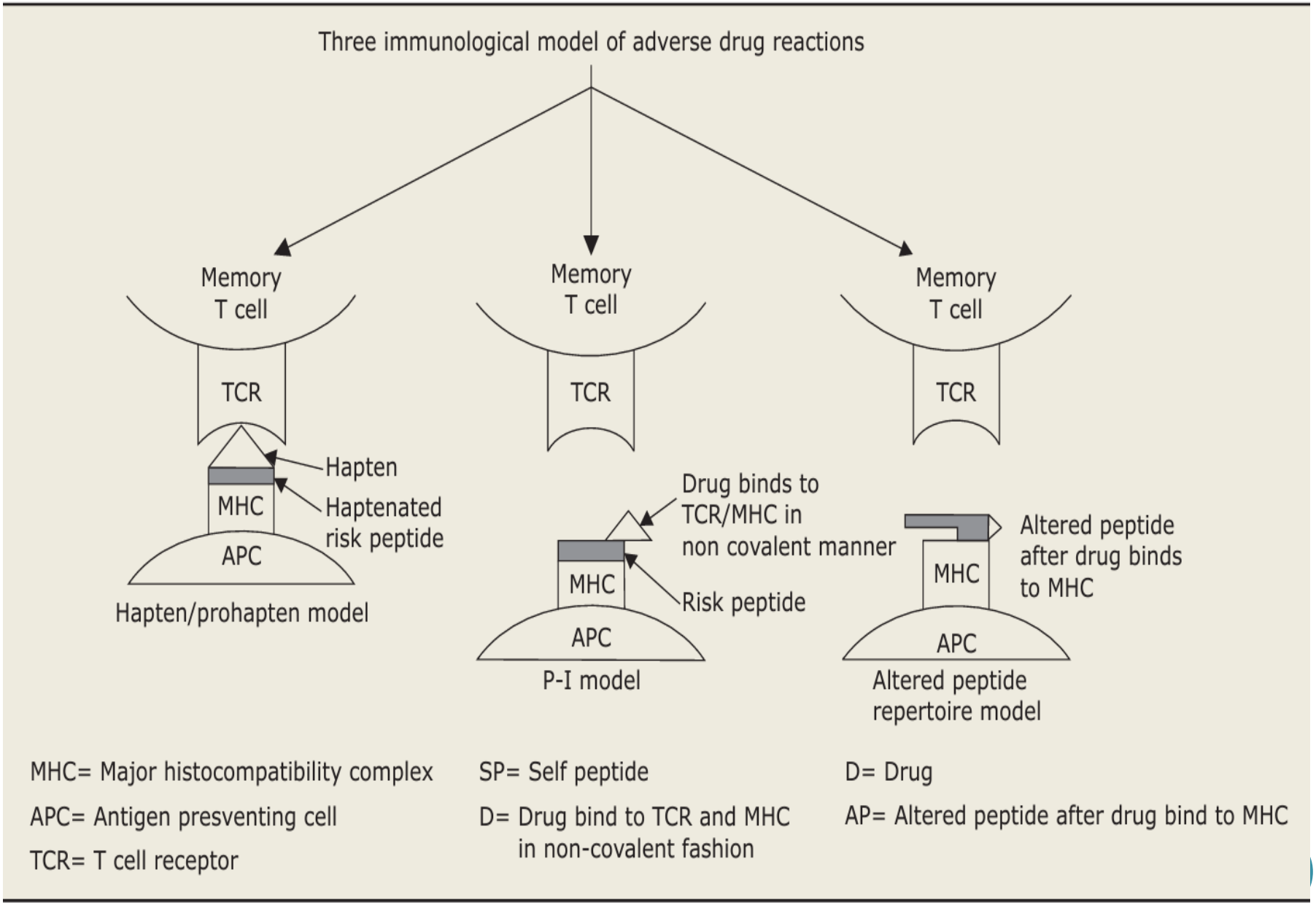


Fig. 3.1: Immunologic models of cutaneous adverse drug reactions.

HLA responses

- HLA DR4 is significantly more common in individuals with hydralazine-related drug-induced lupus than in those with idiopathic systemic lupus erythematosus.

- HLA factors also influence the risk of reactios to Nevirapine, Abacavir, Carbamazepine, Allopurinol & more.

Factors influencing the risk of drug reactions

- Elderly,females
- Boys < 3 yrs & Girls > 9 yrs
- Viral infections – CMV, EBV, HIV.
- Systemic connective tissue disease.
- Oncologic disease & immunosuppressed states.
- Impaired hepatic / renal function.
- Polypharmacy
- Drug- drug & food-drug interactions
- Genetic variations- e.g. slow & fast acetylators,G6PD deficiency.
- HLA grouping- HLA DR4 & drug induced pemphigus.
- Atopic patients.

- Metaboloic & endocrine risk factors-

Obesity, Hypothyroid, Hypoproteinemia.

- Major organ dysfunction-

Liver dysfunction, renal dysfunction, congestive cardiac failure.

Drugs that commonly cause a skin eruption

- Amoxicillin
- Ampicillin
- Antimalarials
- Antitubercular drugs
- Gold
- Pencillamine
- Phenytoin
- Qunidine
- Sulfonamides
- Sulfones
- Sulfonylurea
- Thiazide

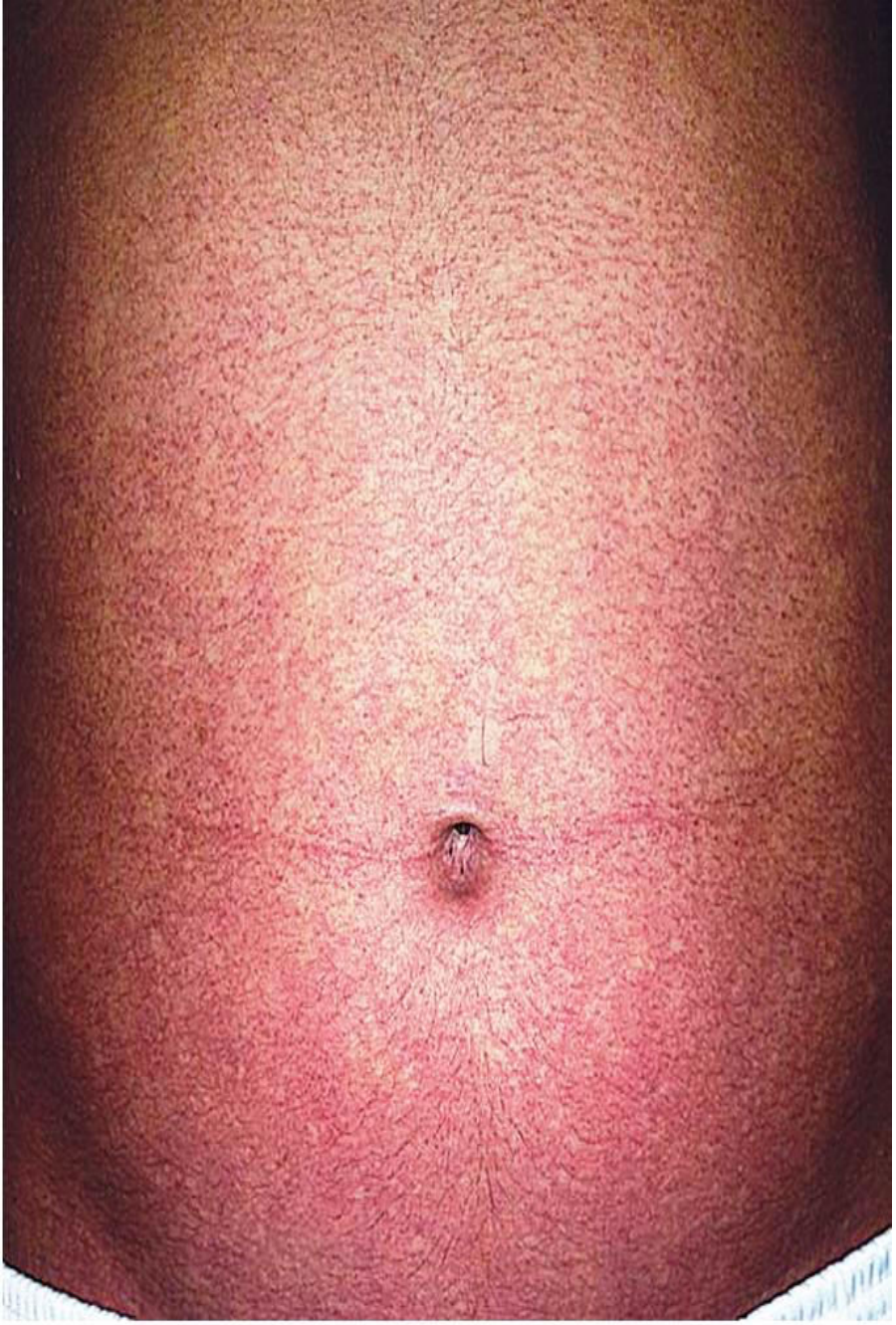


Fig. 37.3: Thrombocytopenic purpuric drug rash to quinine.

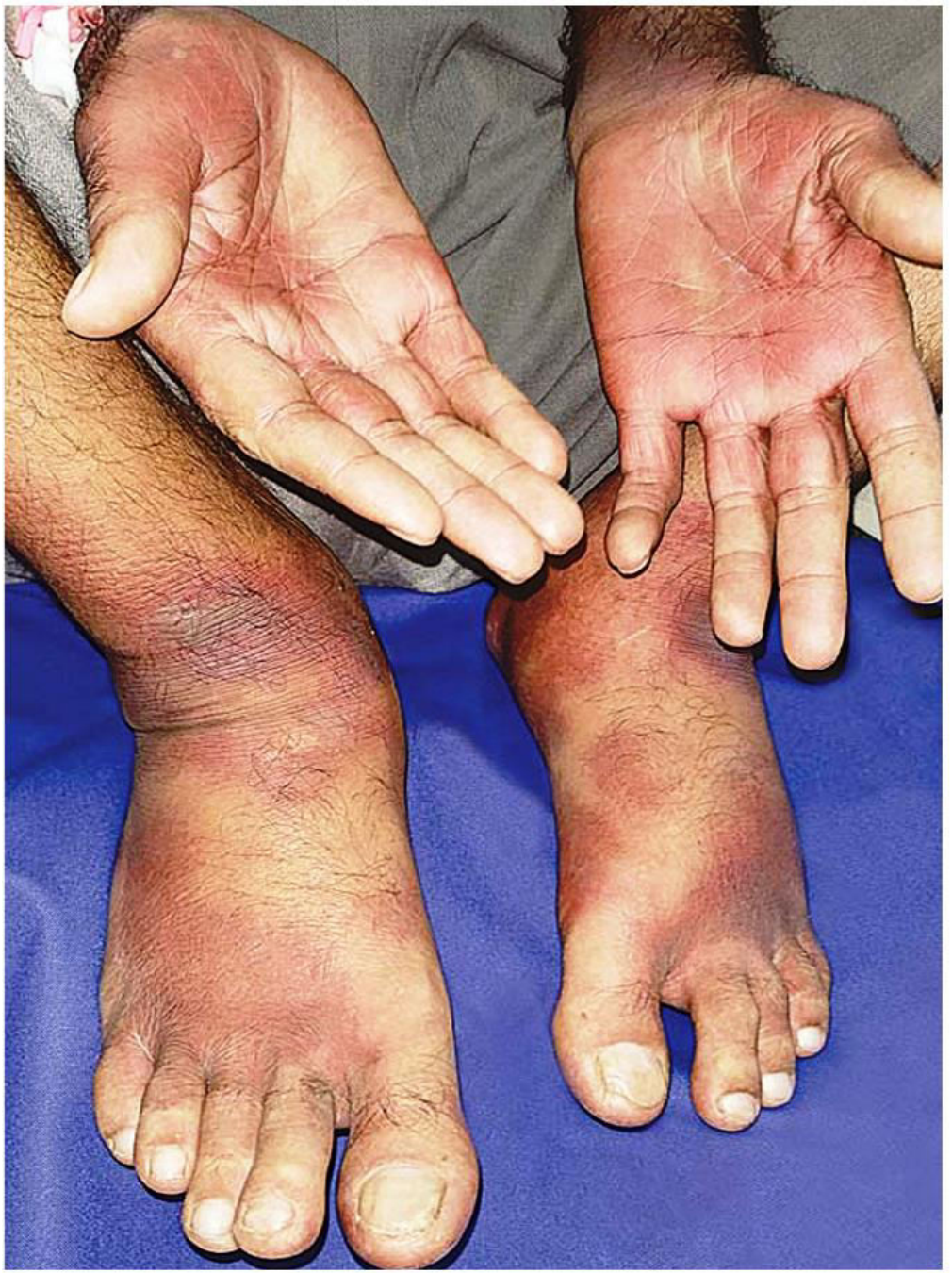


Fig. 37.8: Purpuric rash in glove and socks pattern to sulfasalazine.

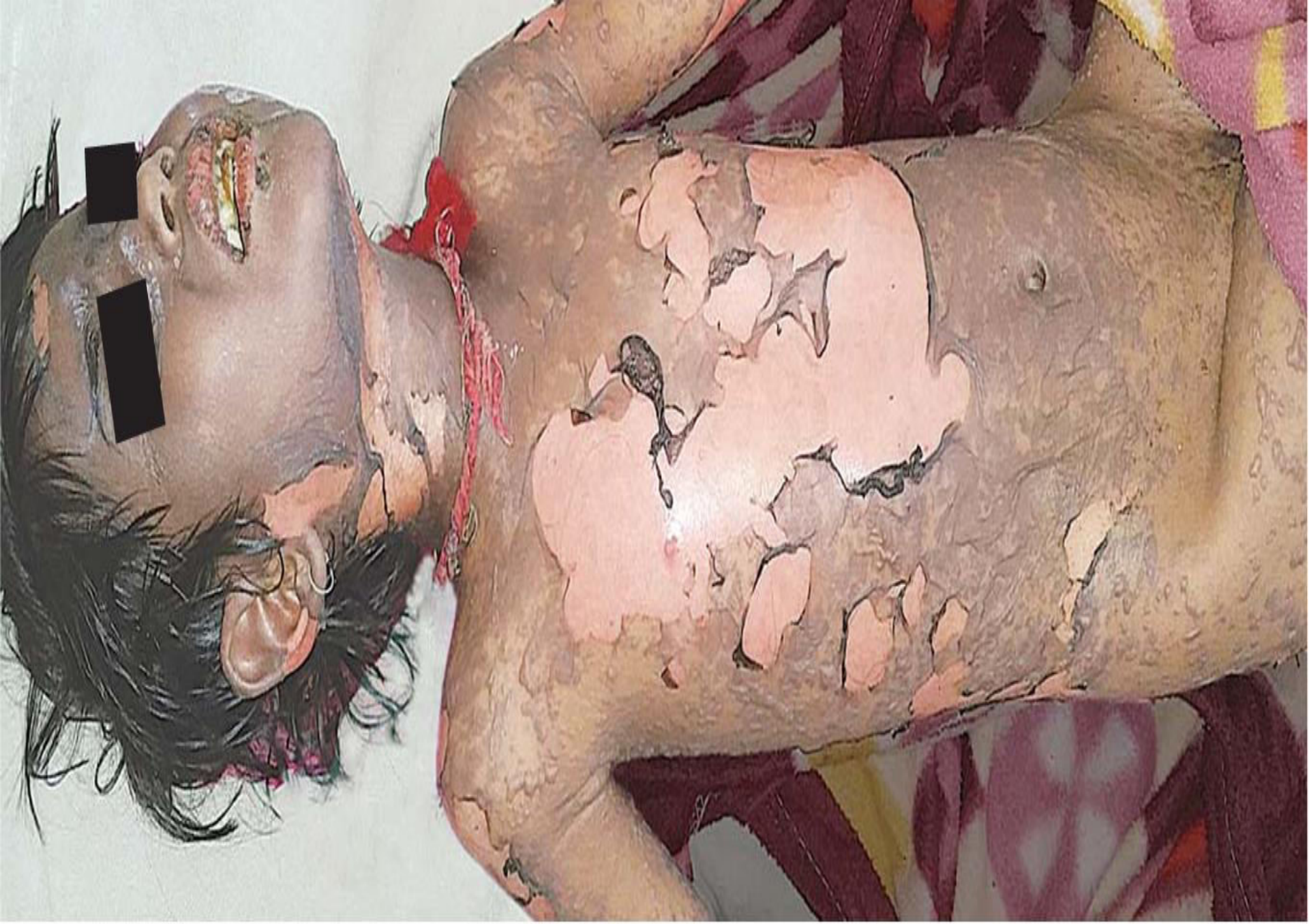


Fig. 33.3: TEN in a child on amoxicillin-clavulanate.

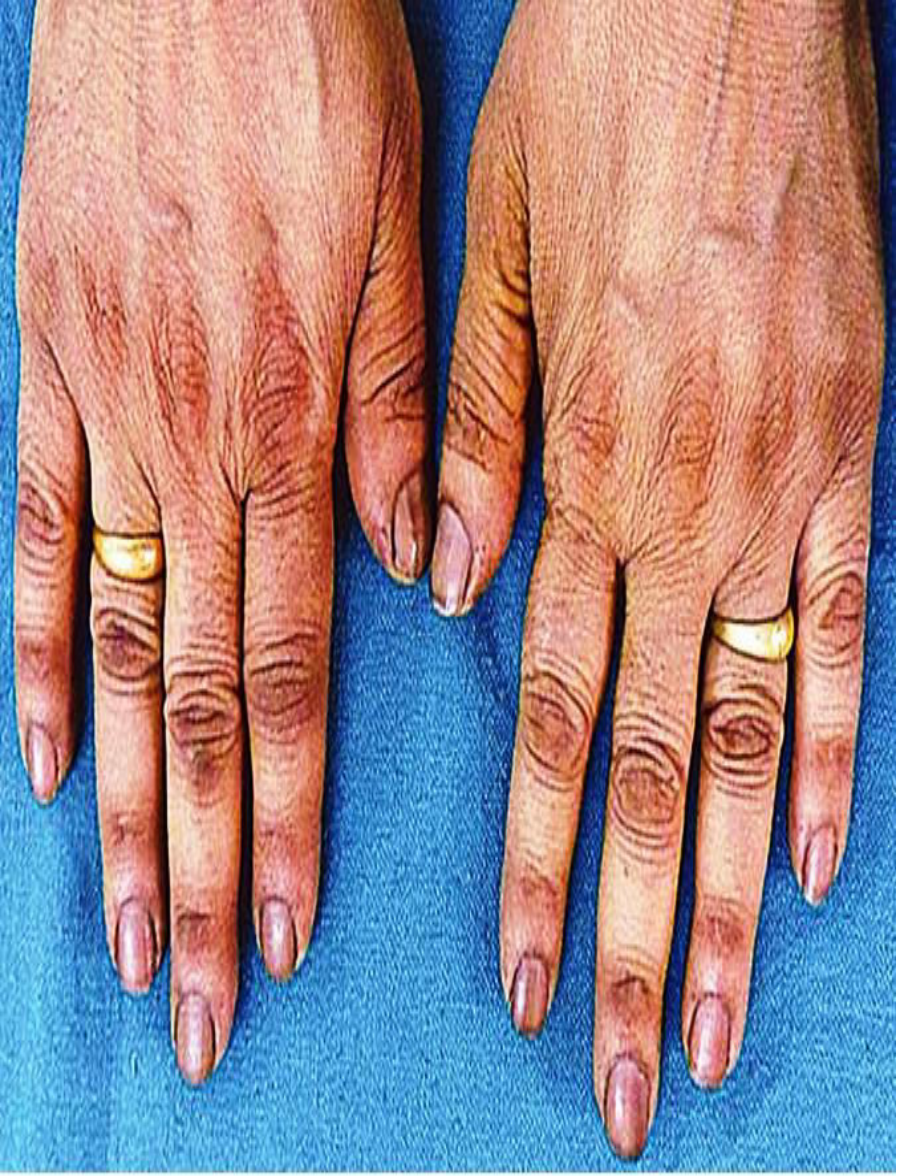


Fig 39.4: Blue black pigmentation of nails in patient of chronic cutaneous discoid lupus erythematosus on hydroxychloroquine for 8 months.

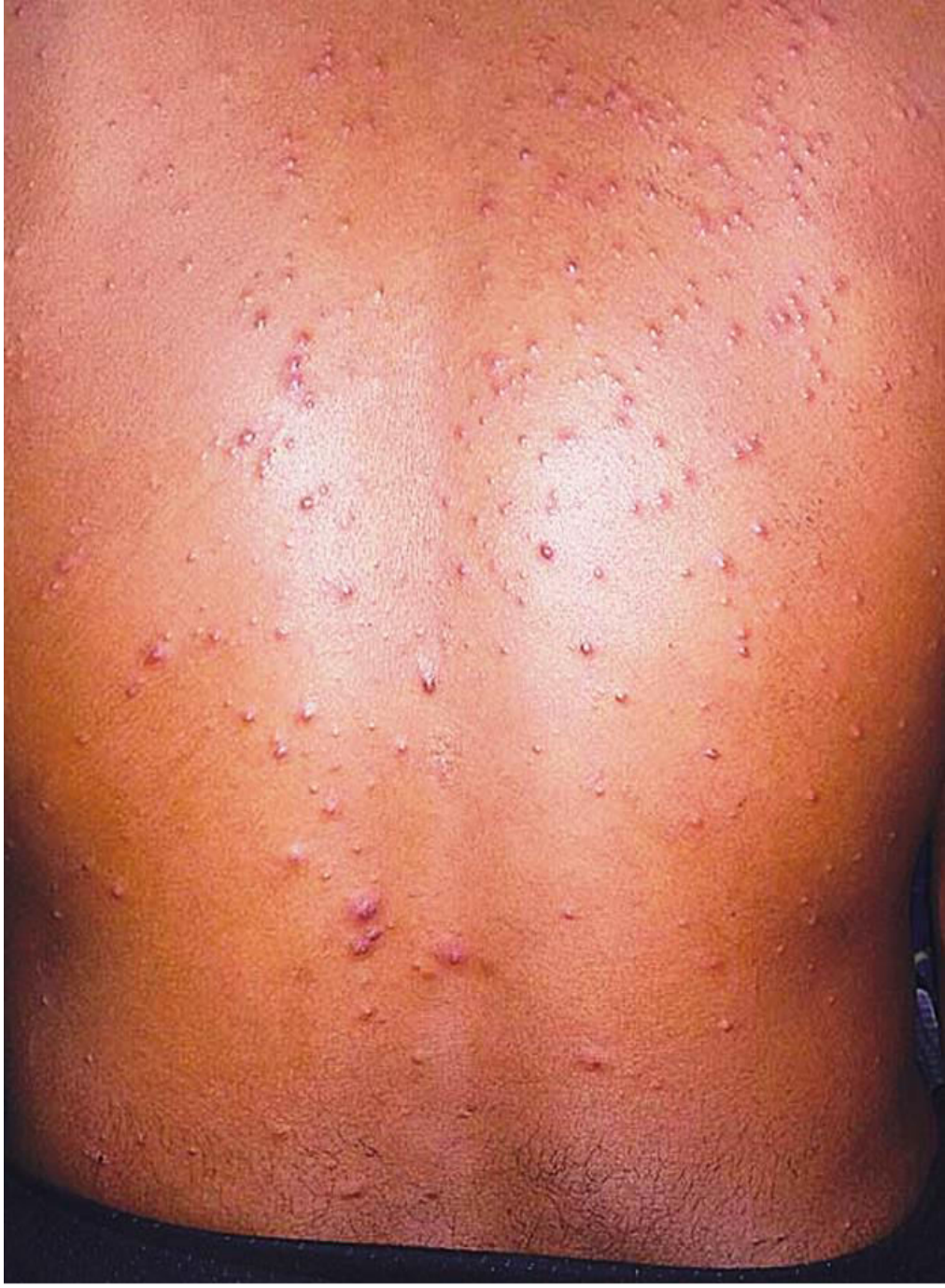


Fig. 33.13: Acneiform rash to isoniazid.

Drugs that commonly cause a serious reaction

- Allopurinol
- Anticonvulsants
- Sulfa drugs
- Captopril
- Furosemide
- NSAIDS
- Pencillamine
- Piroxicam
- Thiazide diuretics

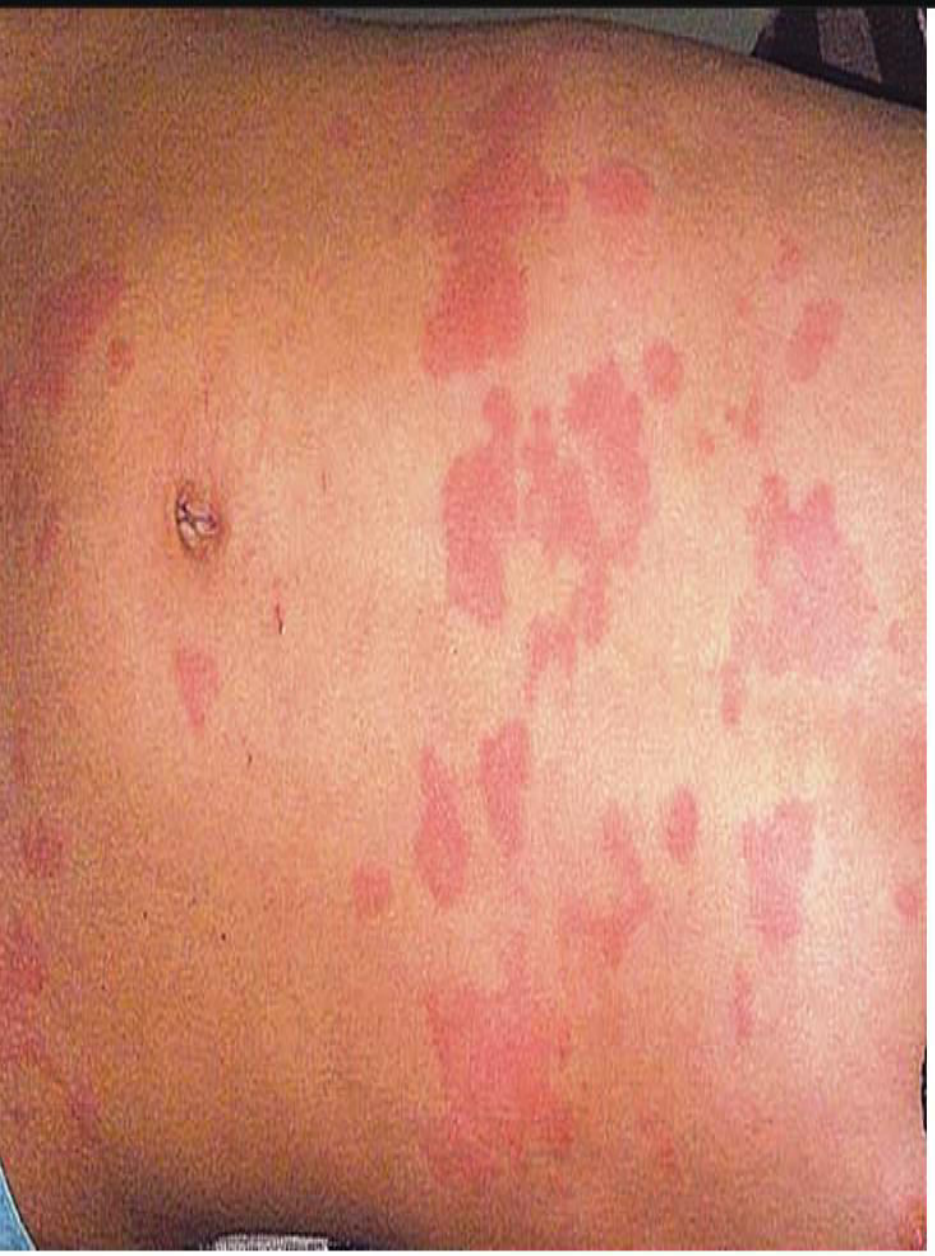


Fig. 36.2: Urticarial rash in a child due to phenobarbitone.

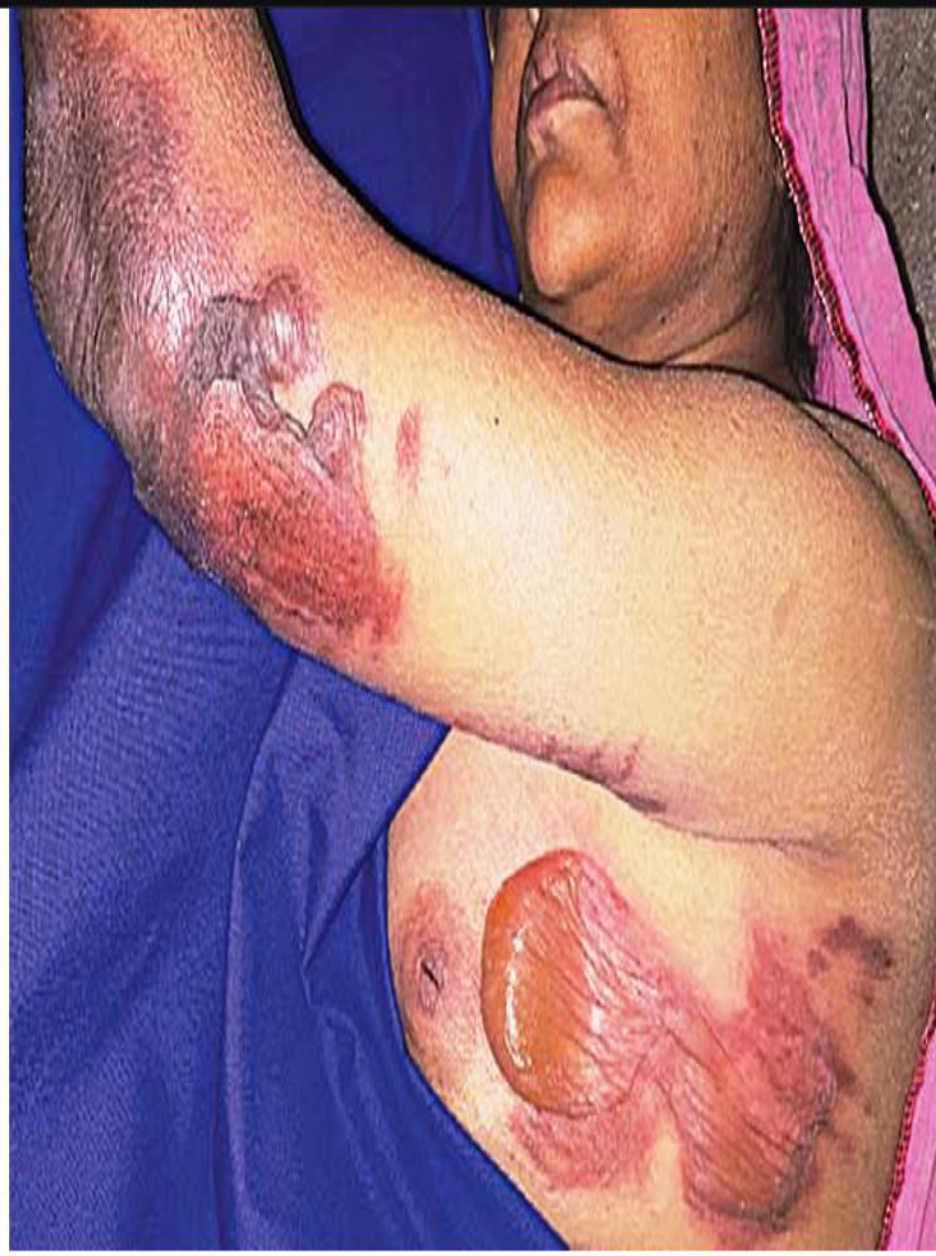


Fig. 36.3: Bullous fixed drug eruption in a female patient taking carbamazepine for trigeminal neuralgia.

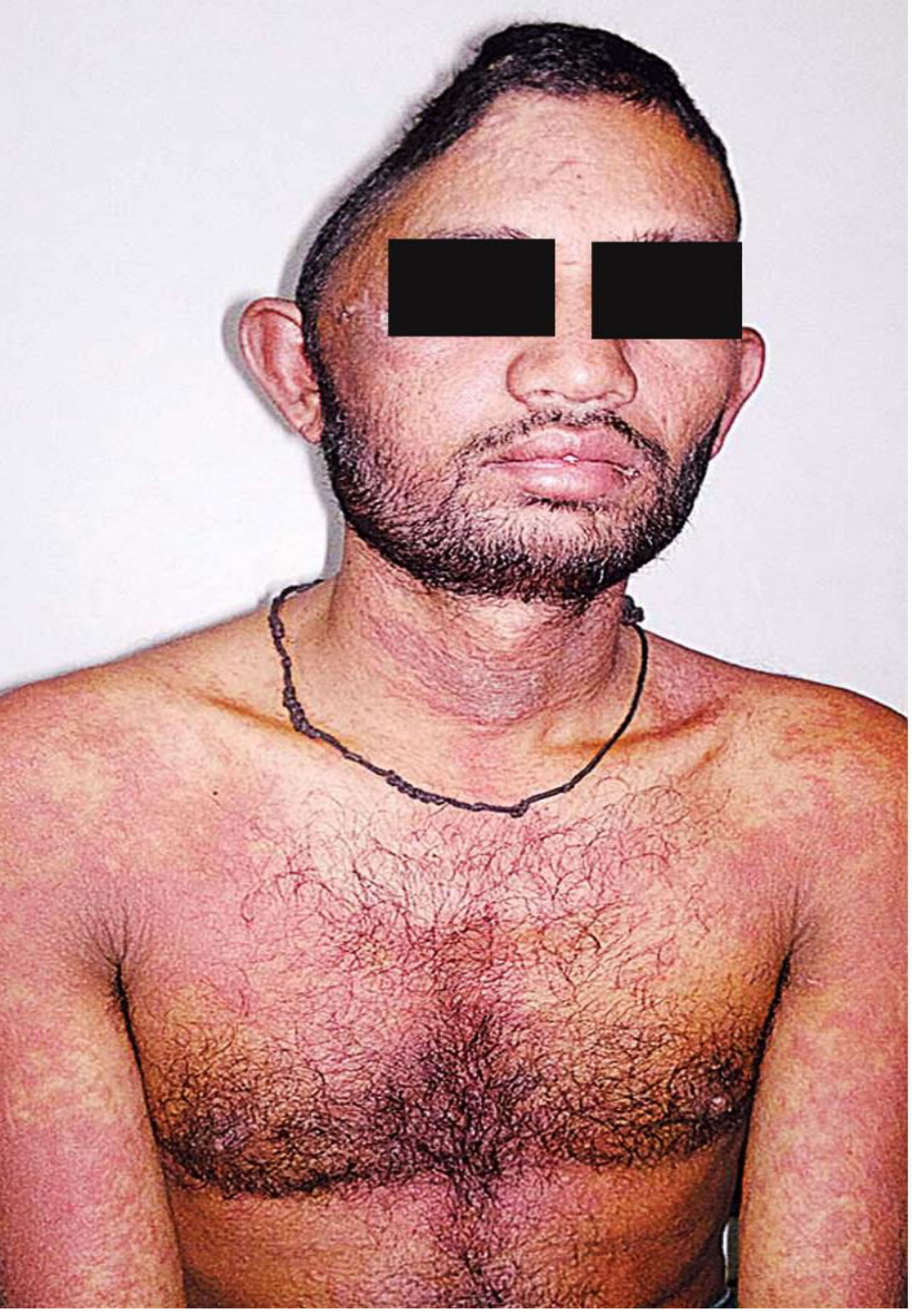


Fig. 36.4: Drug induced hypersensitivity to phenytoin in a young boy who had undergone brain surgery.

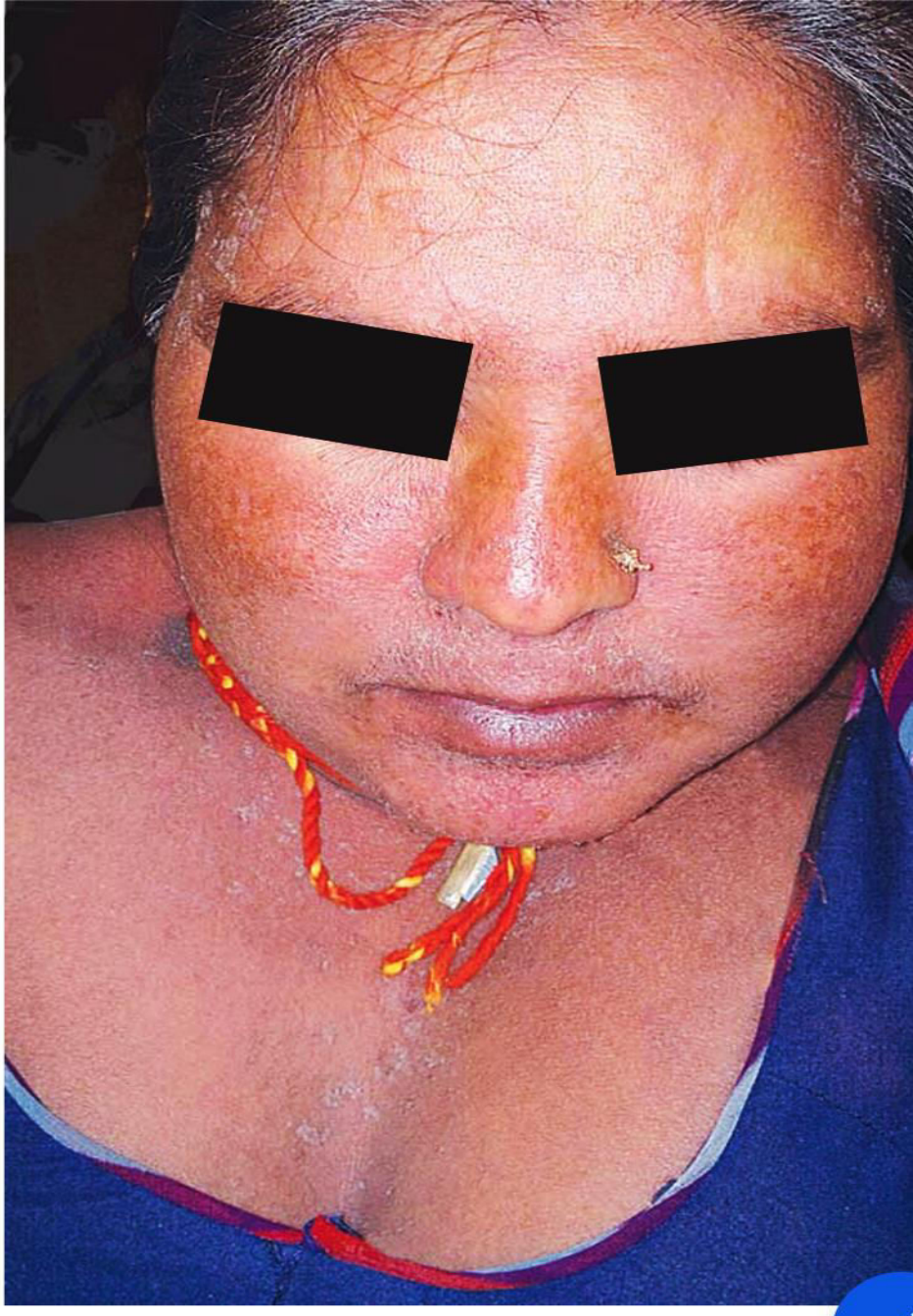


Fig. 36.5: Drug induced hypersensitivity to so valproate in a patient of generalized seizures.

Table 44.1: Types of CADRs based on severity

Nonsevere reactions	Severe reactions (SCARs)
• Maculopapular rash (exanthematous eruption) • Urticaria • Fixed drug eruption • Acneiform eruption • Erythema multiforme	• Angioedema • SJS/TEN • Drug hypersensitivity syndrome • Drug-induced anaphylaxis • SSLR • AGEP • Drug-induced erythroderma

SCAR - severe cutaneous adverse reaction; SJS - Steven–Johnson syndrome; TEN - toxic epidermal necrolysis; SSLR - serum sickness–like reaction; AGEP - acute generalized exanthematous pustulosis.

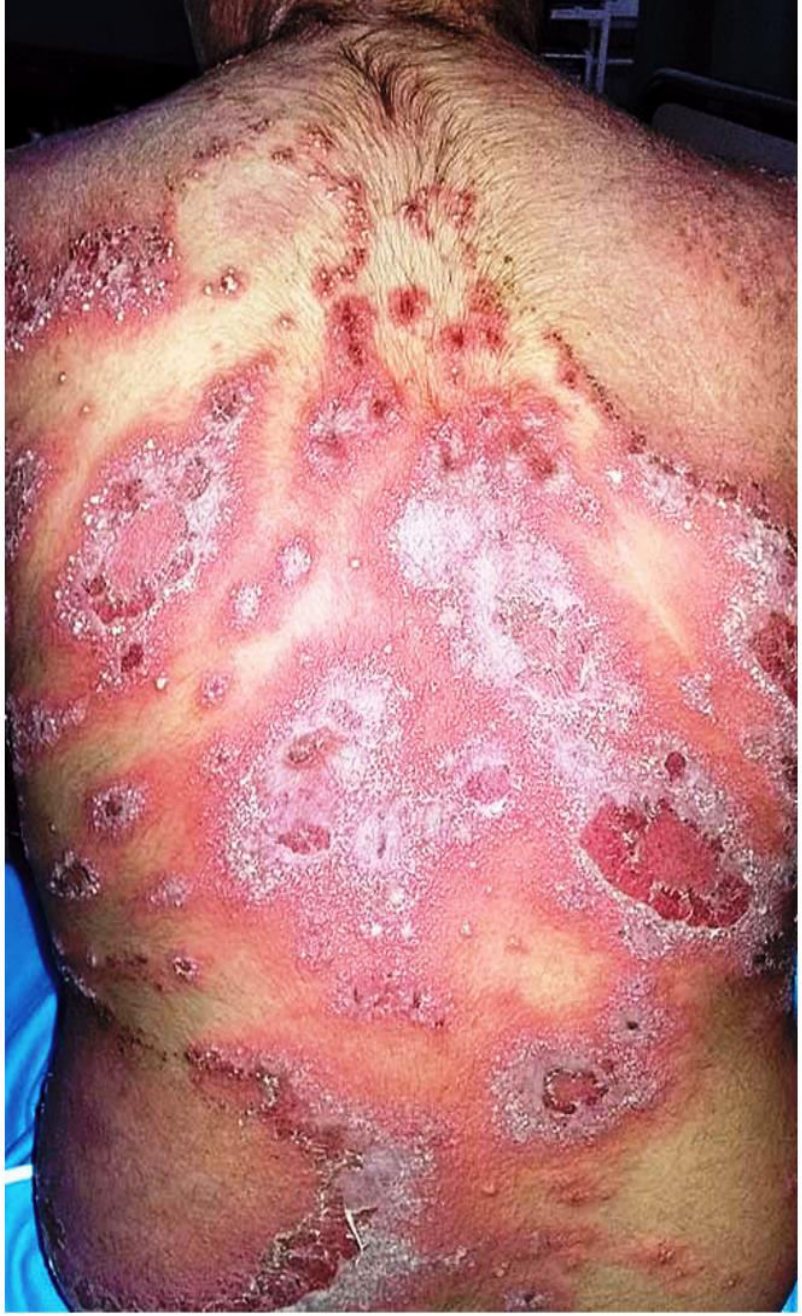
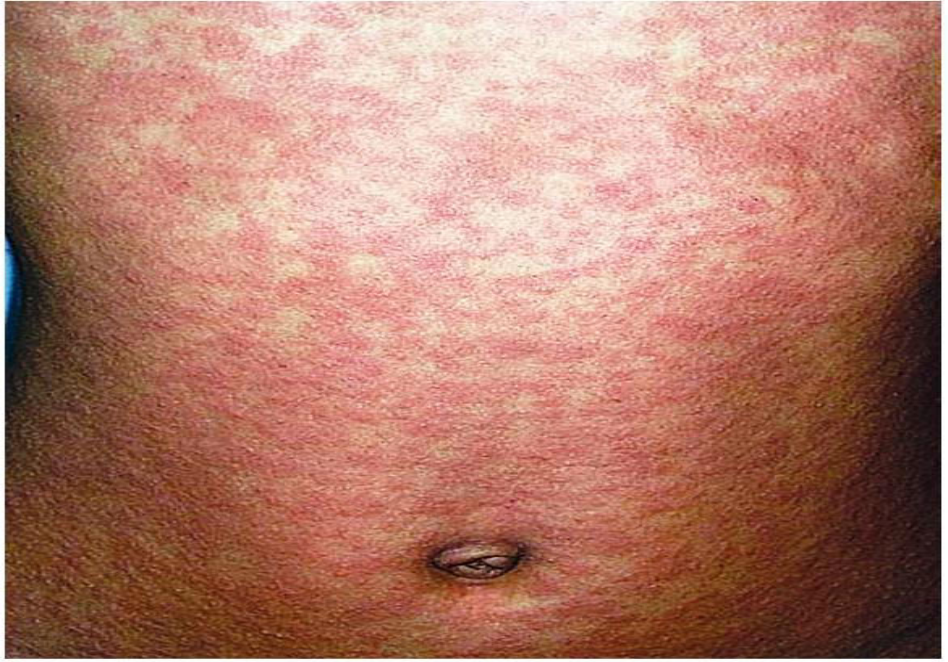


Fig. 32.2: AGEP showing numerous pustules and lakes of pus on back, induced by amoxicillin/clavulanic acid. (Courtesy of Dr. K. Lekshmi Priya, Guwahati.)



33.1: Maculopapular rash in a patient on amoxicillin.

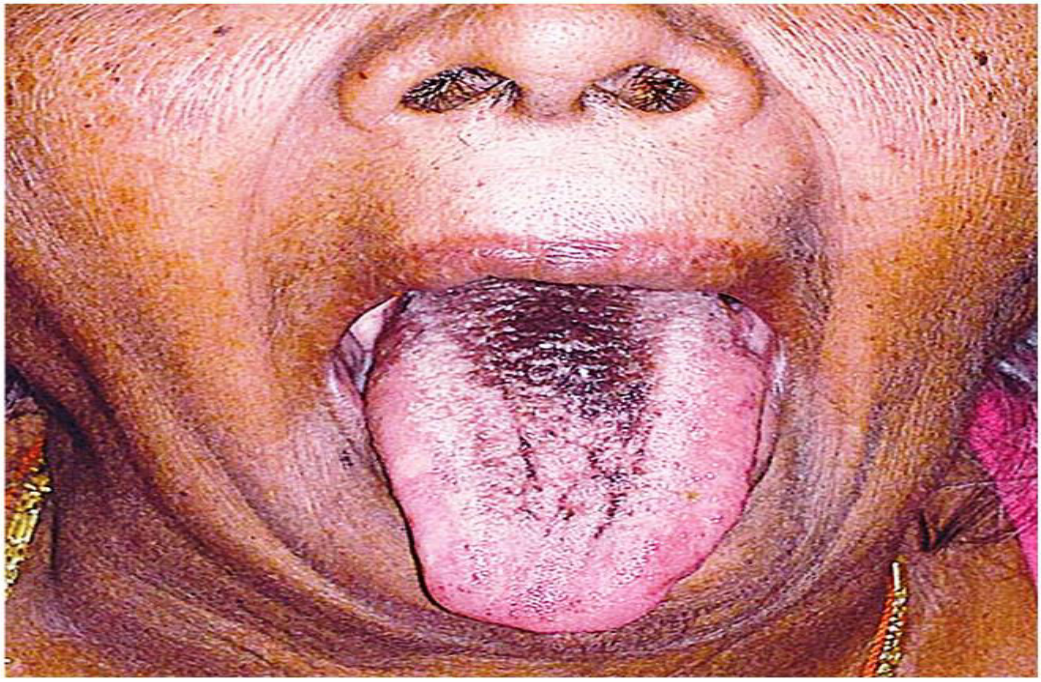


Fig. 33.2: Black hairy tongue in a patient on ampicillin

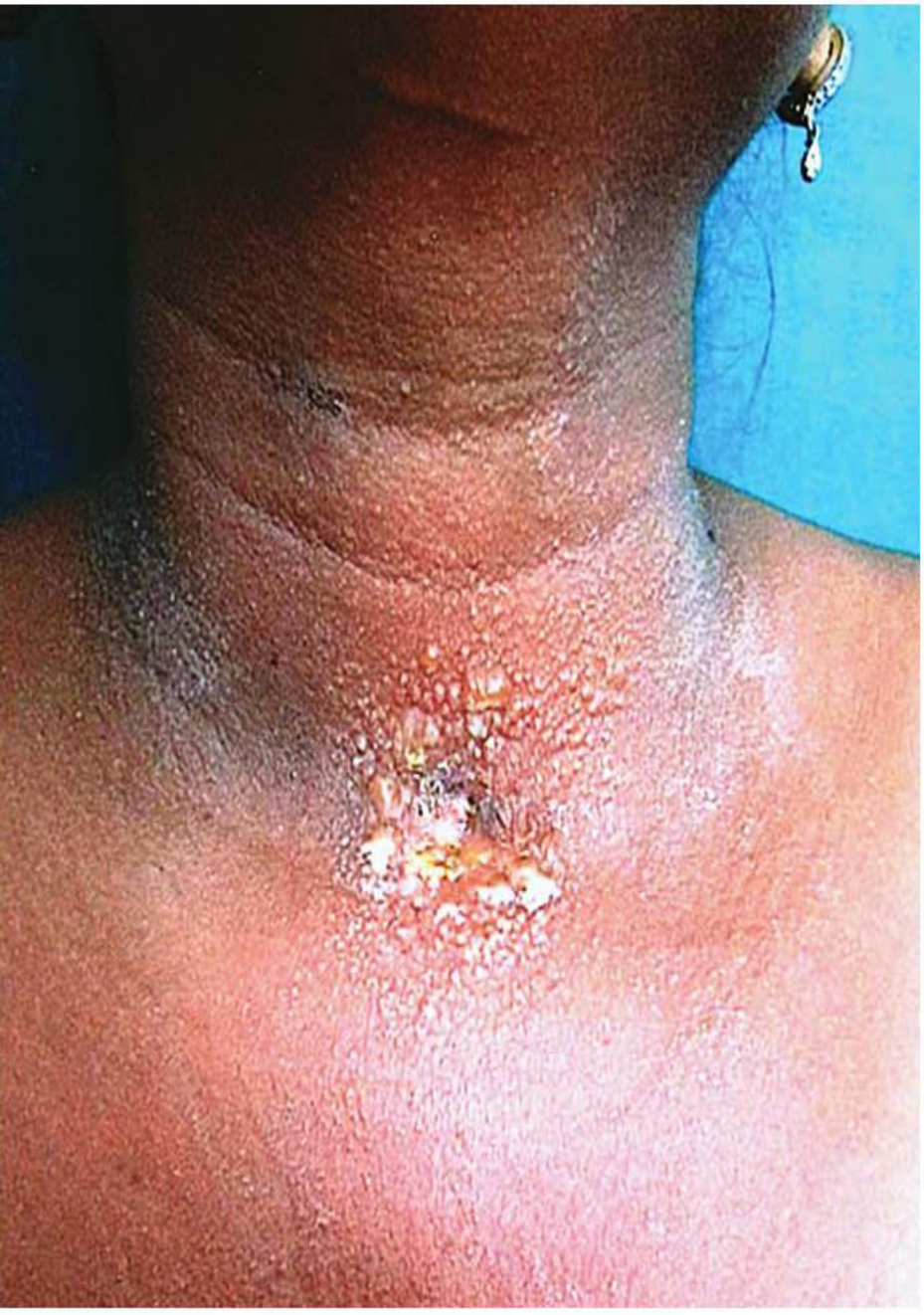


Fig. 33.4: AGEP in a female patient on Cefaclor. (Courtesy of Dr. Bela Shah, Ahmedabad.)

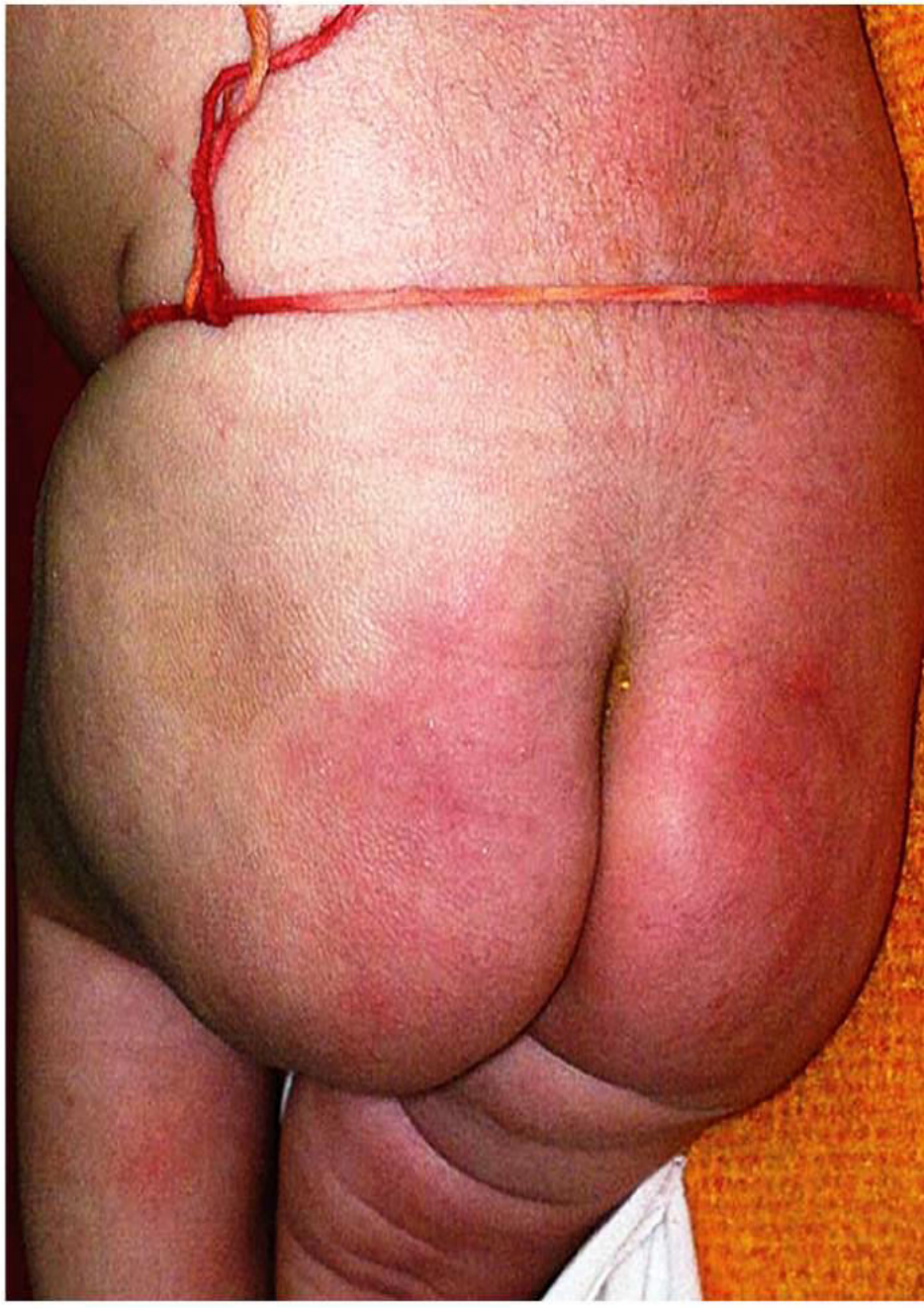


Fig. 33.5: Baboon syndrome to cephalosporin in an infant.

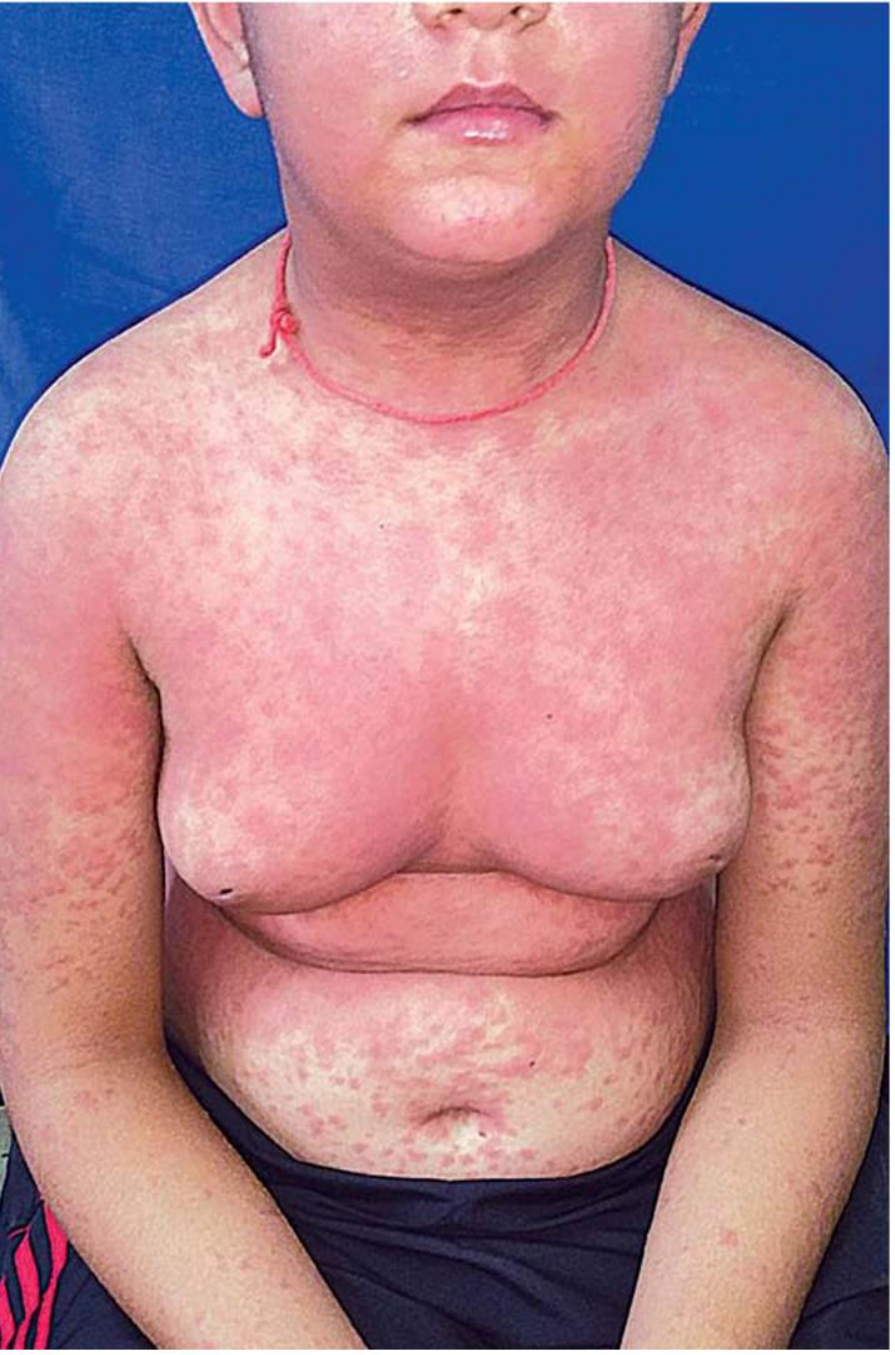


Fig. 31.7: Urticarial lesions in drug reaction with eosinophilia and systemic symptoms (DRESS).

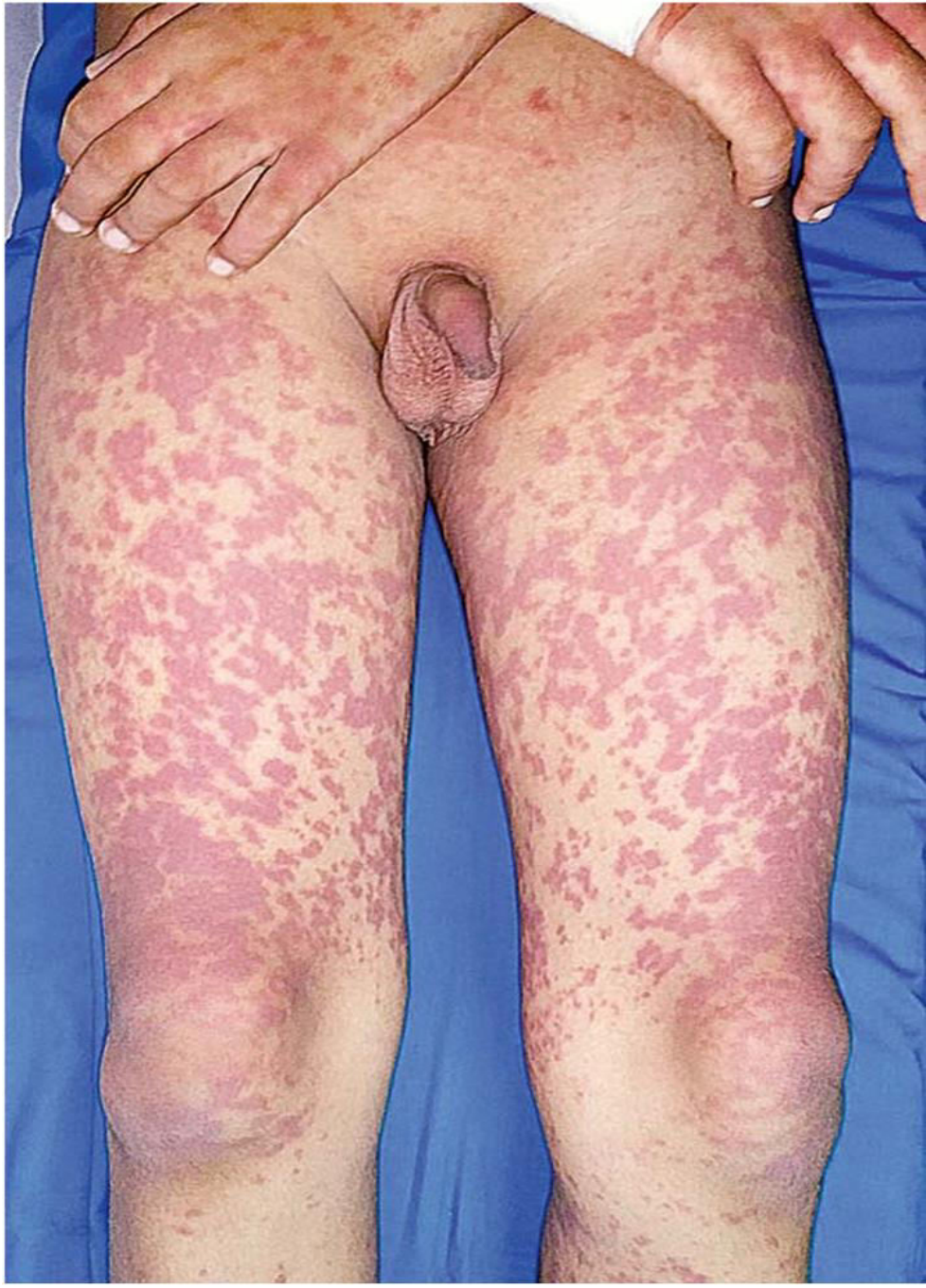


Fig. 31.9: Purpuric rash in drug reaction with eosinophilia and systemic symptoms (DRESS).

Table 44.2: Different morphological pattern of drug reactions with most common causative drugs

Clinical morphology	Types	Common causative drugs
Exanthematous	Simple eruptions	Penicillin, sulfonamides, amoxicillin, antiepileptics
	Hypersensitivity syndromes	Phenytoin, phenobarbitone, carbamazepine, dapsone, allopurinol, antibiotics, lamotrigine
Urticarial	Urticaria/angioedema	Penicillin, NSAIDs, cephalosporins, sulfonamides, ACE inhibitors
	SSLR	Cefaclor, cefprozil, minocycline, infliximab, rituximab
Pustular	Acneiform eruptions	Corticosteroids, iodides, isoniazid, androgens, lithium, phenytoin
	AGEP	β-lactam antibiotics, macrolides
Bullous eruptions	Bullous FDE	Phenolphthalein, NSAIDs, sulfonamides, tetracyclines, lamotrigine
	EM/SJS/TEN	Anticonvulsants, sulfonamides, antibiotics, NSAIDs, dapsone
	Pseudoporphyria	Tetracyclines, furosemide, naproxen
	Pemphigus/BP/LAD	Penicillamine, captopril, penicillin, rifampin, vancomycin, diclofenac, piroxicam
Miscellaneous	NEH, FDE, drug-induced lupus, photosensitivity reactions, lichenoid eruptions, cutaneous pseudolymphoma, drug-induced vasculitis, pigmentary changes, nonscarring alopecia, psoriasiform reactions, pruritus, peripheral neuropathy, hair and nail changes, eruptions from biological therapies, anticoagulant-induced skin necrosis	Procainamide, hydralazine, isoniazid, minocycline, phenytoin, penicillin, sulfonamides, chloramphenicol, dopamine, mannitol, sodium bicarbonate, warfarin, antineoplastic drugs, antiretroviral drugs

SSLR - serum sickness–like reaction; AGEP - acute generalized exanthematous pustulosis; FDE - fixed drug eruption; EM - erythema multiforme; SJS - Stevens–Johnson syndrome; TEN - toxic epidermal necrolysis; BP - bullous pemphigoid; LAD - linear IgA disease; NEH - neutrophilic eccrine hidradenitis; NSAIDs - nonsteroidal anti-inflammatory drugs; ACE - angiotensin-converting enzyme.

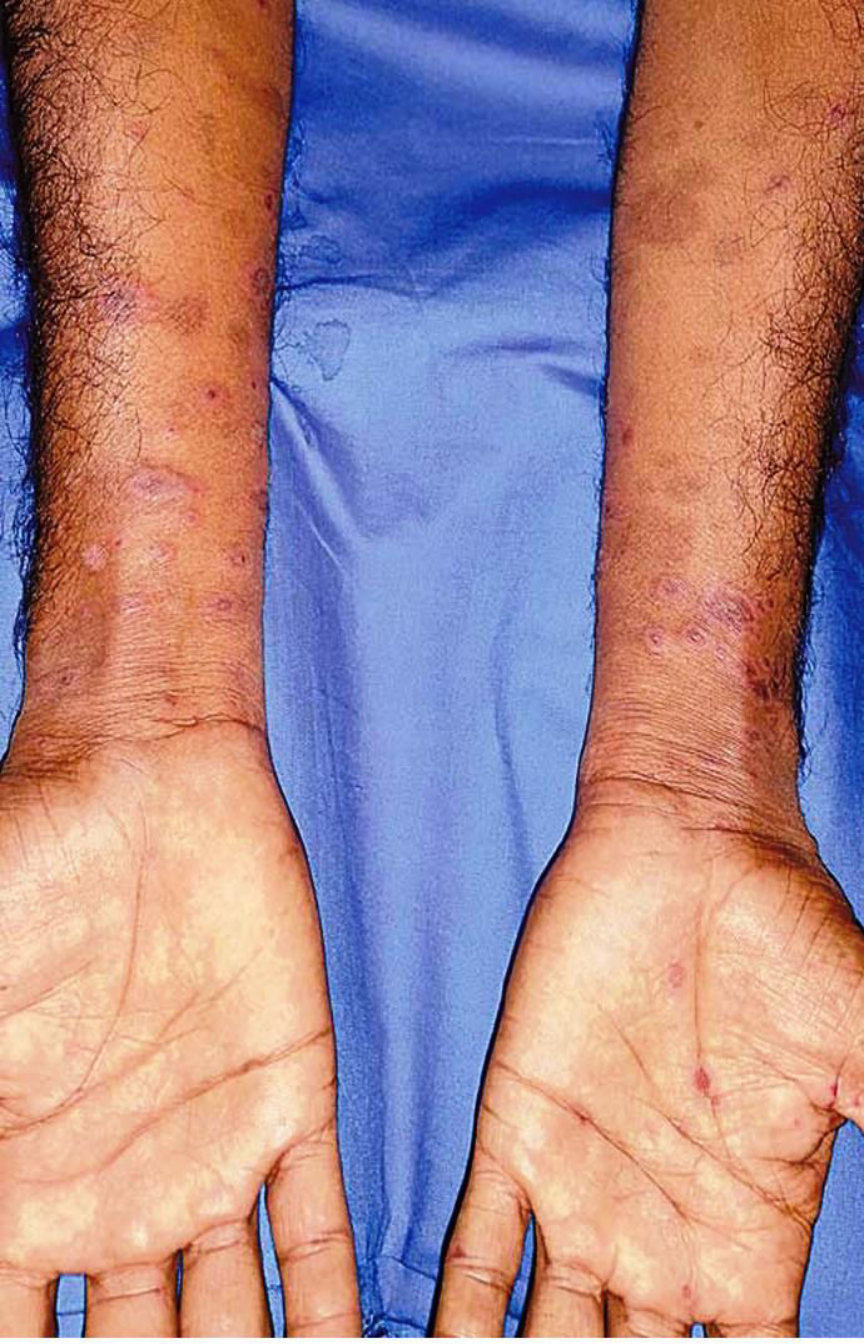


Fig. 33.10: Erythema multiforme with typical target lesions in a patient taking co-trimoxazole.

Fig. 33.11: Lesions of FDE affecting arm and genitals in a patient on co-trimoxazole.

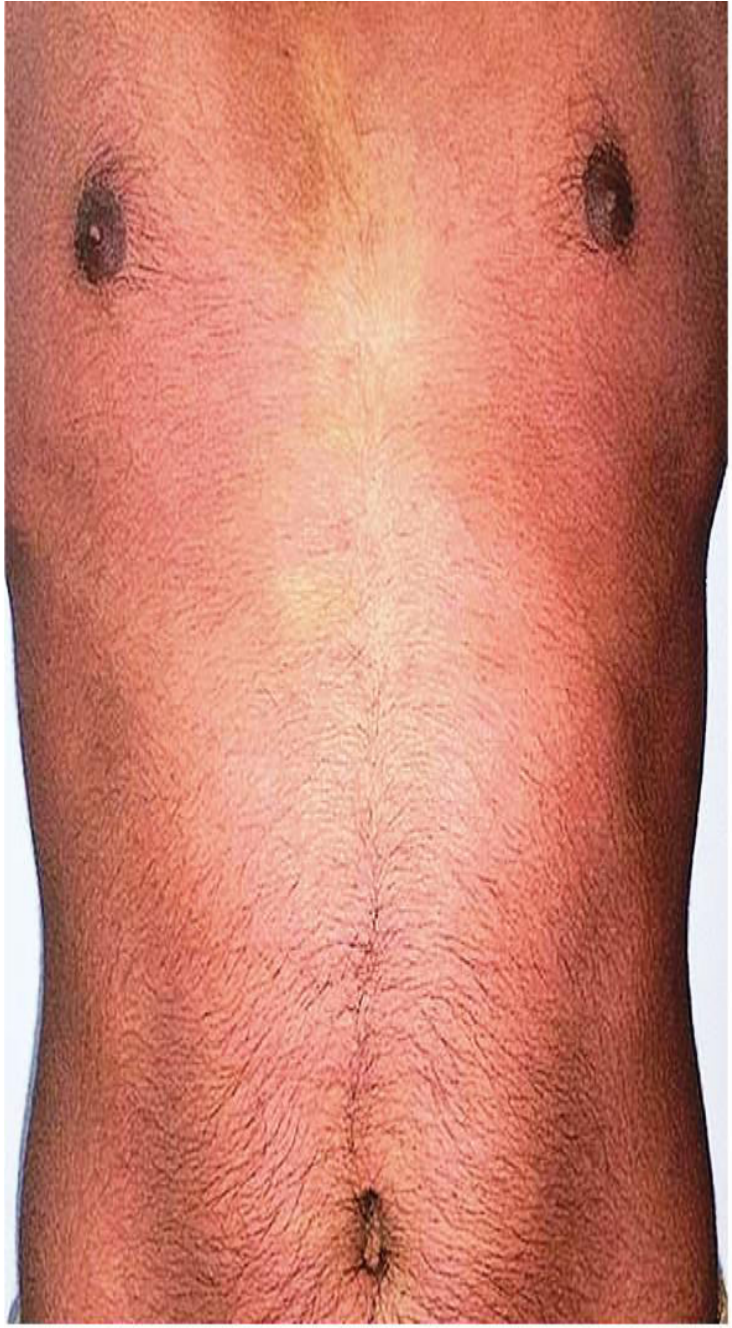


Fig. 35.2: Exanthematous rash on trunk due to telmisartan.

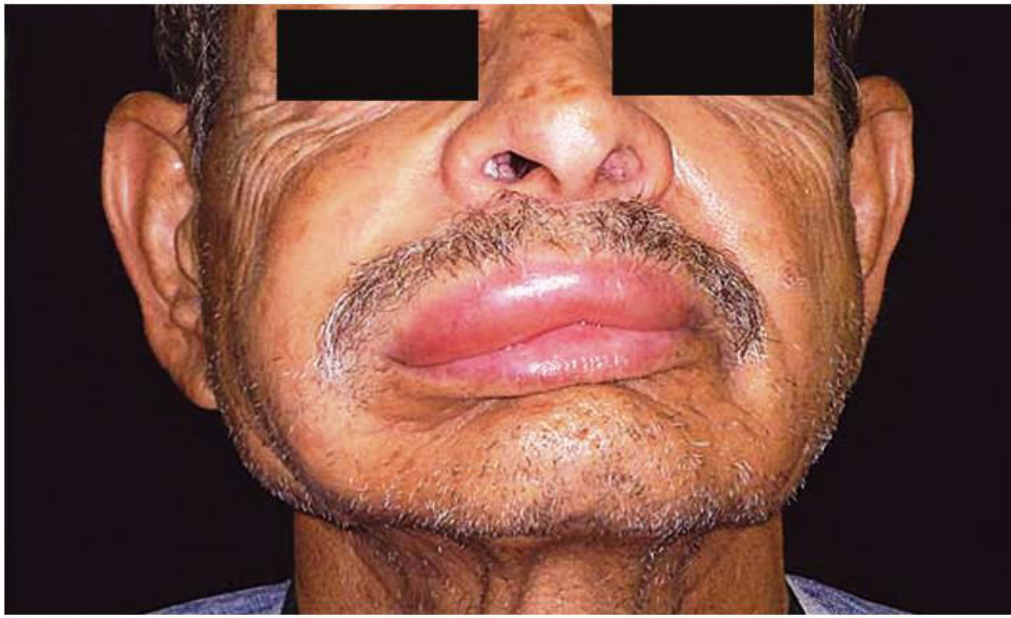


Fig. 35.3: Angioedema in a patient receiving Ramipril for last 9 months. The patient had several episodes in past. Improvement occurred after substitution with Nebivolol.

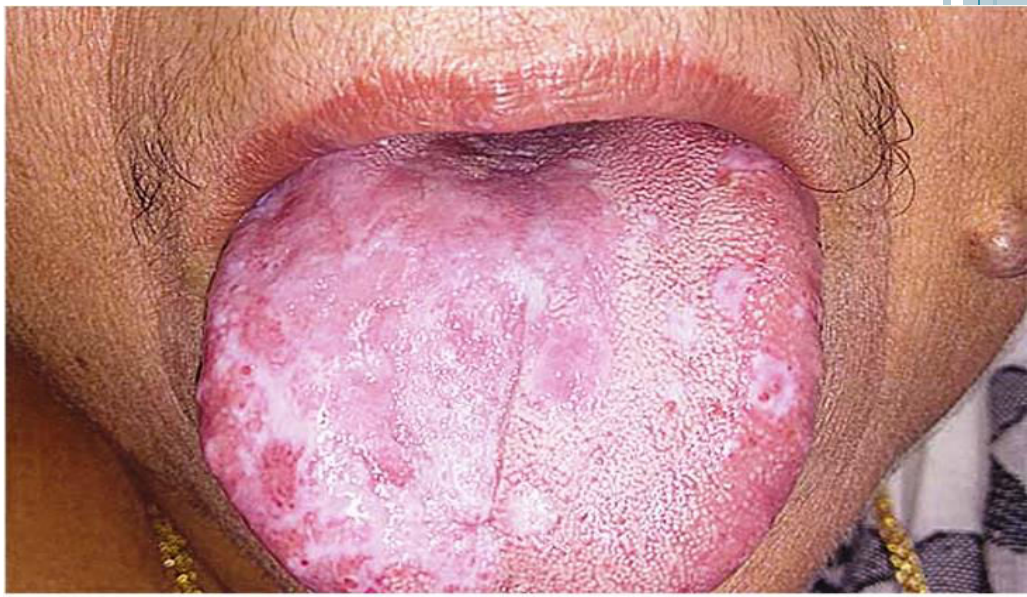


Fig. 35.8: Oral lichenoid lesions in a hypertensive patient on amlodipine and telmisartan.

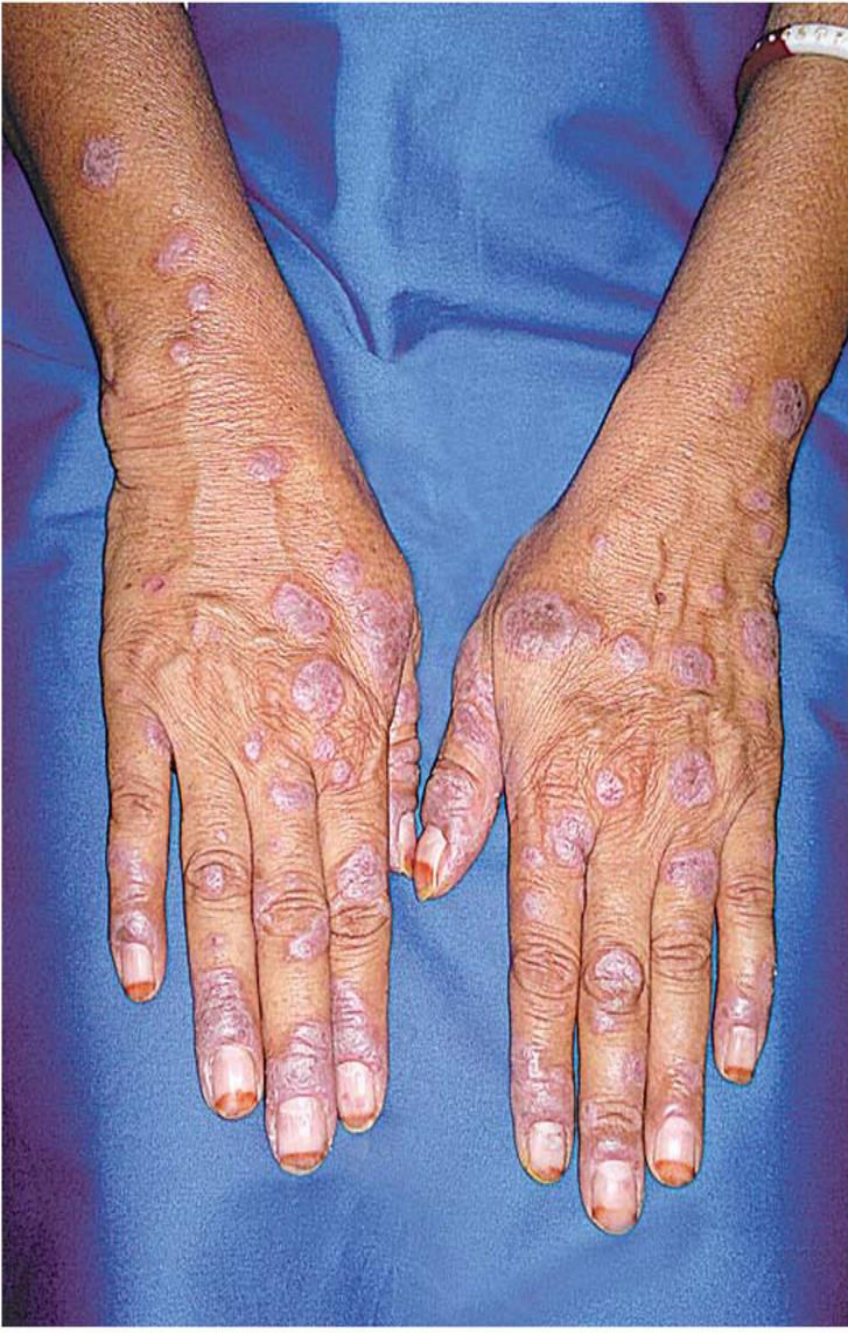


Fig. 35.5: Lichenoid reaction in a patient taking amlodipine.

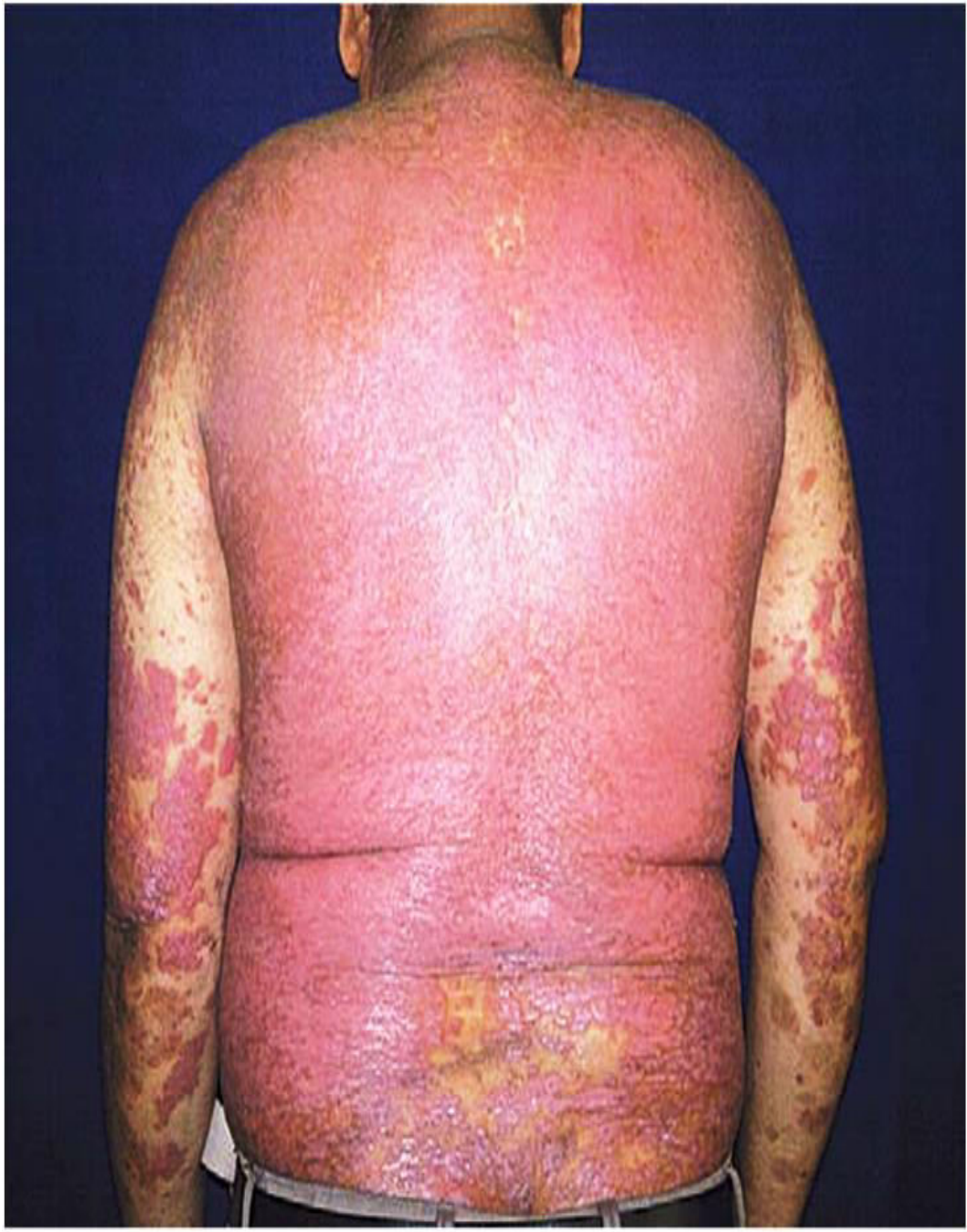


Fig. 35.6: Psoriasiform rash in a patient on captopril.

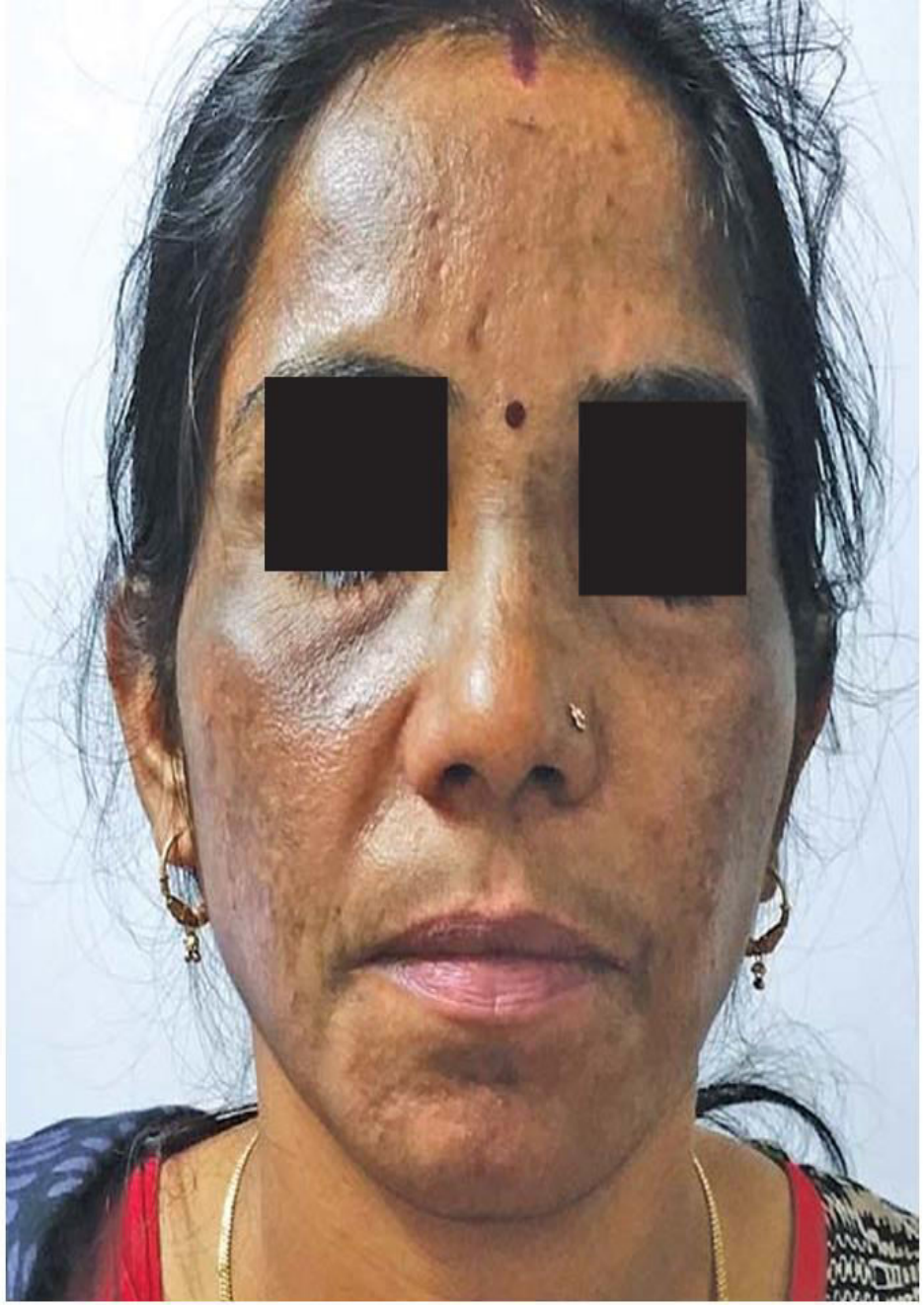


Fig. 40.1: Facial pigmentation in a patient on cyclophosphamide.

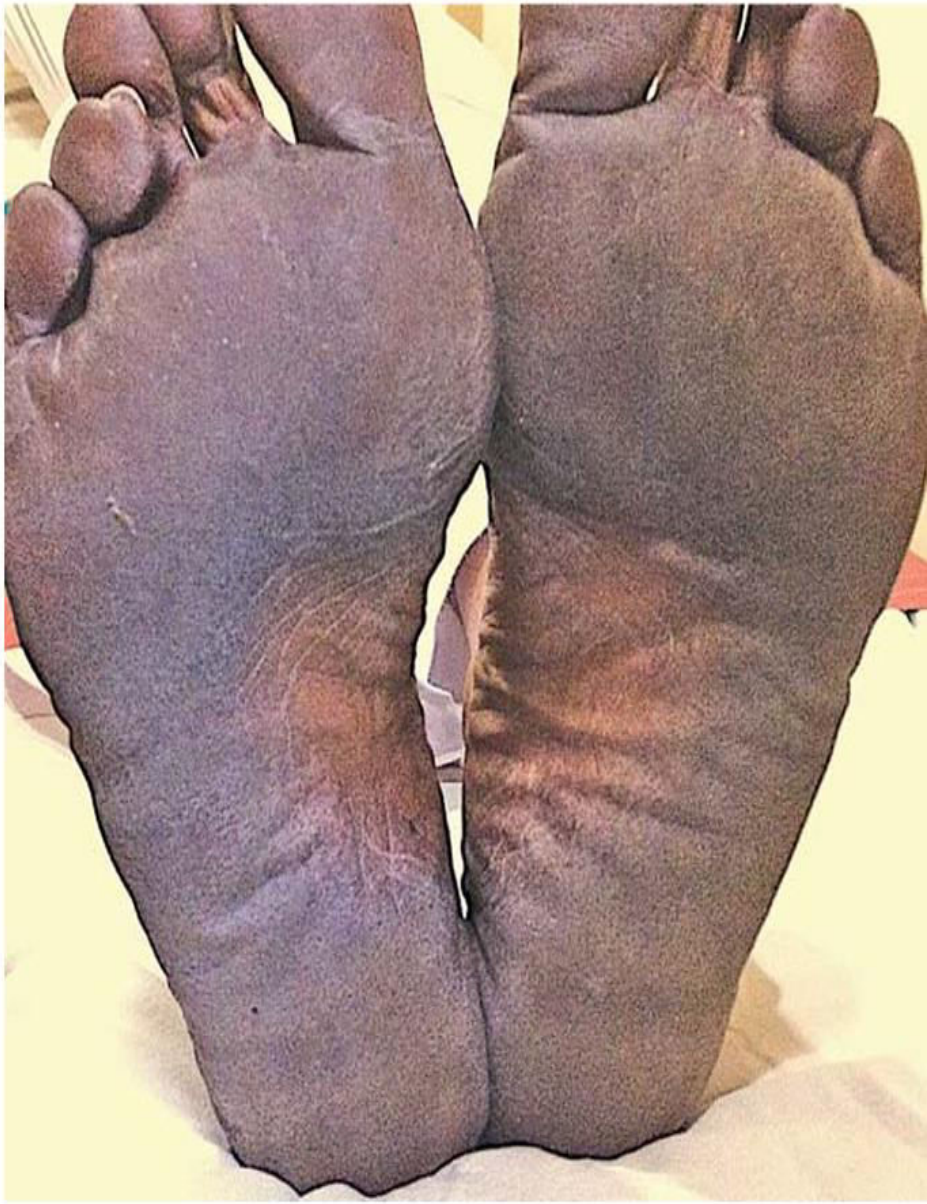


Fig. 40.2: Pigmentation on soles due to busulfan in a patient with chronic myelogenous leukemia.

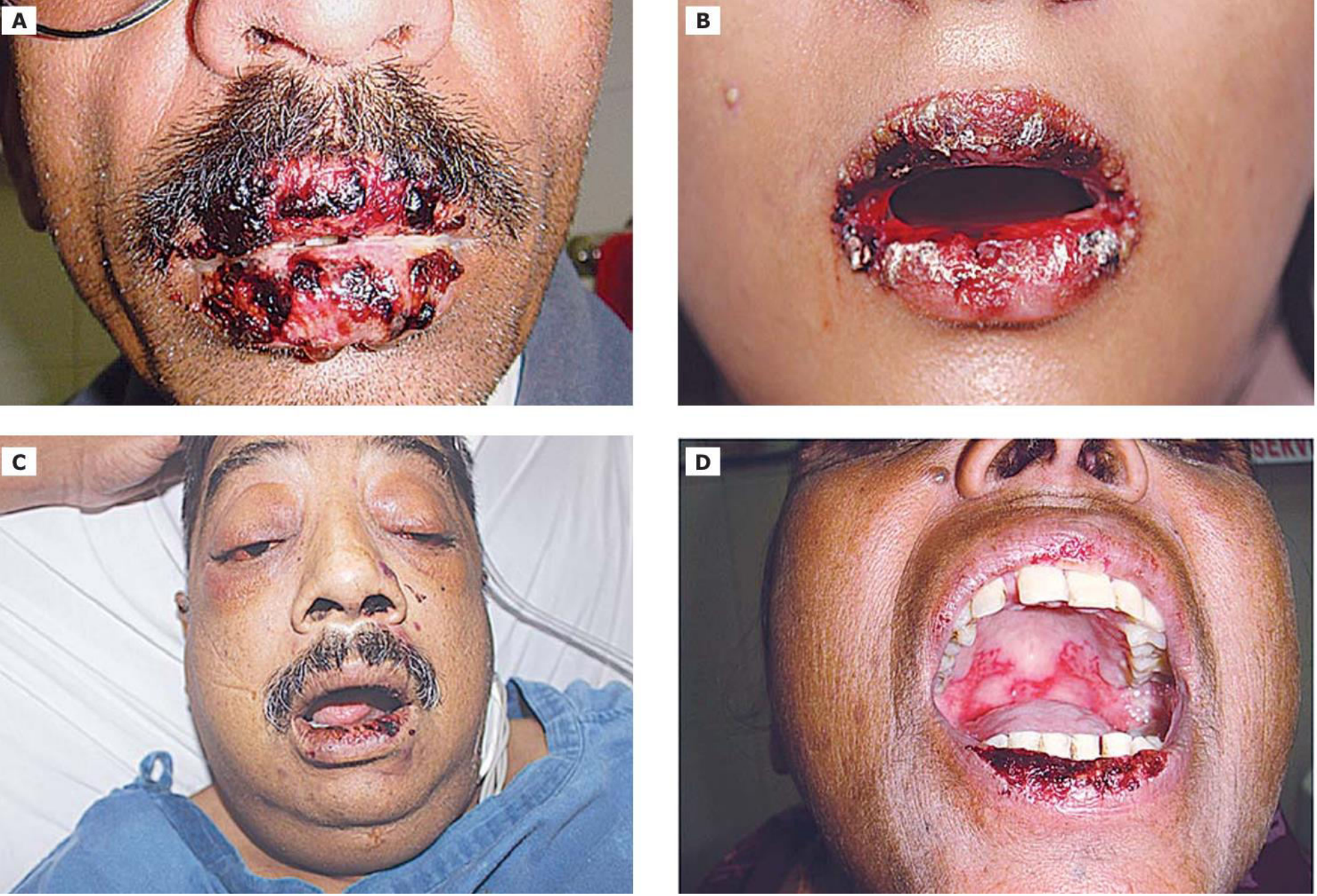
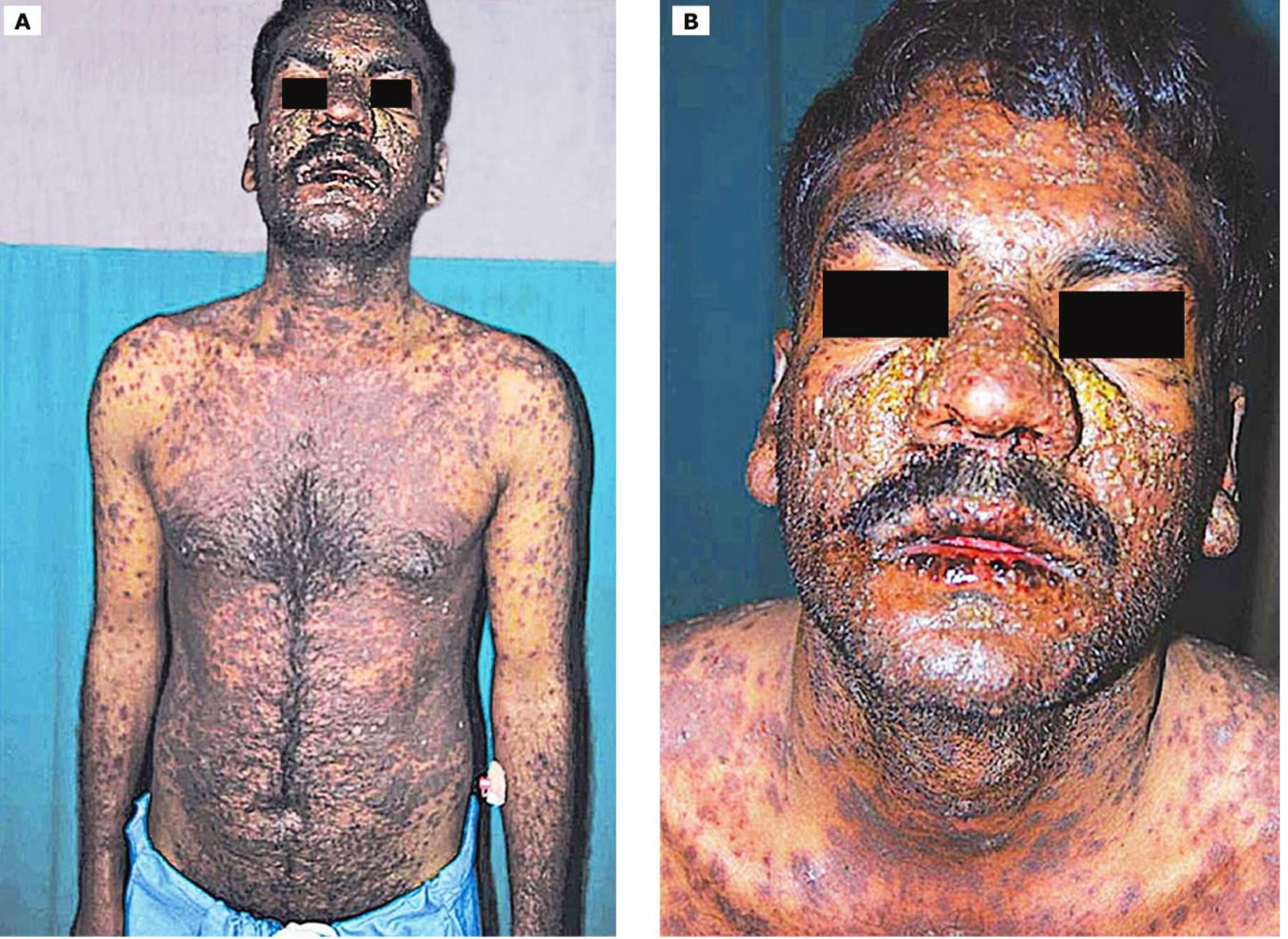


Fig. 30.4: (A) Characteristic hemorrhagic crusting of lips in SJS due to carbamazepine; (B) Hemorrhagic crusting and scaling of lips in a child with SJS on cotrimoxazole; (C) Conjunctival and oral mucosal involvement in SJS; (D) Hemorrhagic crusting on lips with oral erosions, in SJS patient.



30.5: (A) Extensive skin, lip and eye involvement of SJS-TEN in a patient on phenobarbitone; (B) A close up view of same patient with extensive skin and mucosal involvement.

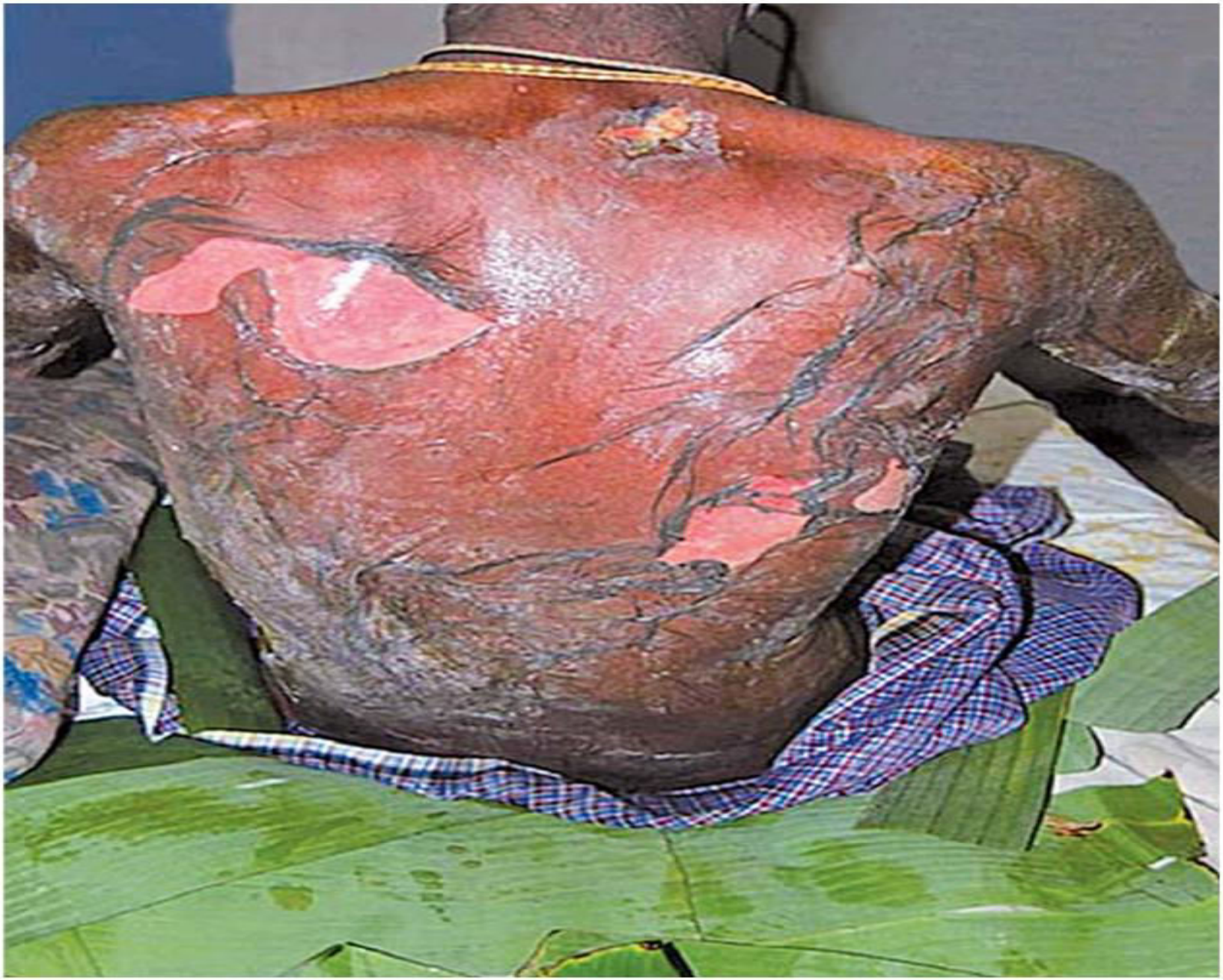


Fig. 30.6: Sheets of skin loss in TEN with banana leaf used for skin care.

- Clinical pointers that indicate serious drug reaction-

- CUTANEOUS / MUCOCUTANEOUS:
- Extensive cutaneous involvement (75%)
- Widespread bullae & skin detachment
- Purpura
- Skin necrosis
- Atypical large lesion
- Erosions of oral & genital mucosa

- EXTRACUTANEOUS-
- Fever > 38.5◦c
- Pharyngitis , dysphagia or dyspnoea
- Hepatosplenomegaly
- Anxious / toxic look of patients
- Hematological alteration
- Impaired hepatic or renal functions.

REACTIONS LOCALIZED TO SITES OF INJECTIONS OF MEDICATIONS	
Corticosteroids	Dermal atrophy, lipoatrophy, telangiectasias, deposits, hypopigmentation
Vitamin K	Erythematous plaque, often annular (Fig. 21.25); morpheaform plaque (Texier disease)
Heparin	Necrosis, ecchymosis, erythematous plaques, urticaria (see Ch. 23)
Low-molecular-weight, calcium-containing heparin	Calcinosis cutis
Iron	Brown discoloration, hyperpigmentation
Vitamin B_{12}	Pruritus, morpheaform plaque
Hyaluronic acid, silicone	Swelling, granulomatous reaction (see Ch. 94)
Aluminium-containing vaccine	Nodules, foreign body reaction
Thimerosal-containing vaccine	Allergic contact dermatitis
Interferon*	Vasculopathy with necrosis, development of plaque of psoriasis, lupus-like reaction
Interleukin-2	Lobular panniculitis, granulomas

CUTANEOUS SIDE EFFECTS OF INSULIN INJECTIONS

Immediate hypersensitivity

- Local reaction (erythema, pruritus)
- Urticaria, angioedema
- Anaphylaxis (rare)

Delayed hypersensitivity

- Reaction at injection sites (erythema, induration)
- Morbilliform eruption (rare)
- Acute generalized exanthematous pustulosis (AGEP) (rare)
- Exfoliative dermatitis (rare)

Lipodystrophy

- Lipoatrophy (occurs less frequently with rapidly absorbed analogue insulins, e.g. insulin lispro)
- Lipohypertrophy

Clinical Approach To A Suspected Drug Reaction

HISTORY CHECKLIST

- Review patient drug list
  - Prescription as well as nonprescription drugs
  - Vitamins, supplements, pain relievers, laxatives, oral contraceptives, and native and indigenous medications
- Create a drug and rash "timeline"
  - Drug related: Time of initiation, dose and duration administered, time of stoppage of drug

CLINICAL EXAMINATION CHECKLIST

- Prodromal symptoms: Malaise, fever, flu-like symptoms
- Morphology of rash-macular, papular, maculopapular, pustular, urticarial, vesiculobullous, pityriasiform, erythroderma, eczematous, purpuric
- Distribution of rash: Generalized, localized, flexural (e.g. SDRIFE)
- Pruritus: More often seen when the rash is drug related
- Mucosal involvement: Single/multiple mucosae
- Palms and soles involvement
- Hair and nail involvement
- Systemic signs: Gastrointestinal, respiratory, hepatic, pulmonary, neurologic

Lab evidences

Lab tests are often done to exclude other differentials. There are no specific tests that point to a drug reaction. Tests that raise a strong suspicion of a drug reaction include the following:

- Eosinophilia
- Leukocytosis
- Raised ESR
- Histopathology: eosinophilic response
- Anti-histone antibody in drug-induced lupus erythematosus (LE)
- In vitro and in vivo testing of suspected drugs

Causality assessment

- To be done by experts (dermatologist, clinical pharmacist, trained physician)
- Naranjo probability scale
- World Health Organization -Uppsala Monitoring Centre (WHO–UMC) scale

Drug withdrawal

Drug dechallenge, rechallenge (not to be done in severe ADRs-SCAR)

- Reporting to appropriate authorities

Rash related

Onset of rash, progression, associated signs and symptoms

- Identify temporal correlation between the introduction of drug and appearance of rash
- History of similar reactions in the past
- Family history of reactions to similar drugs
- Foods that may have precipitated the drug reactions

Pharmacovigilance

Box 7.1: General criteria for diagnosis of cutaneous adverse drug reaction

- The patient's symptomatology is consistent with a drug reaction.
- The patient was administered a drug known to cause such symptoms.
- The temporal sequence of drug administration and appearance of symptoms are consistent with a drug reaction.
- Other causes of the symptomatology are effectively excluded.
- Laboratory data are supportive of an immunologic mechanism to explain the drug reaction (not present or available in all cases).

Clinical history – what do we ask?

- Review patient's complete medication list.
- Interval between induction of drug & onset of eruption.
- New drugs started within preceding 3 months, especially those within 6 weeks, for most cutaneous eruptions.
- Route, dose, duration & frequency of drug administration.

- Use of multiple courses of therapy and prolonged administration (risk of allergic sensitisation)
- Any improvement after drug withdrawal & any reaction with re-administration
- History of co-morbidities, viral infections.
- Intake of other drugs
- Family history of drug allergy
- Document any history of previous adverse reactions to drugs or foods.
- Consider alternative etiologies(e.g. viral exanthems & bacterial infections)

Causality assessment

- In pharmacovigilance, most reports concern suspected reactions.
- In practice – very few reports are certain but most are possible & probable.

WHO – UMC Causality assessment

- This includes the following 4 criteria

1. Time relationships between drug use & adverse event
2. Presence / absence of other competing causes (medications, disease process itself)
3. Response to drug withdrawal or dose reduction (dechallenge)
4. Response to drug readministration (rechallenge)

- **BOCQUET'S CRITERIA**(termed DRESS in 1996)- requires meeting the following 3 features.
- 1) Skin eruption.
- 2) Blood eosinophilia (>1.5 X10,000/micro litre) or the presence of atypical lymphocytes
- 3) Internal organ involvement, including lymphadenopathies (>2cm in diameter), hepatitis (liver transaminases value more than twice the upper normal limit), interstitial nephritis, and interstitial pneumonia or carditis.
- Found to be sipmle to use and appropriate to diagnose DRESS syndrome in clinical practice. Lymphocyte and eosinophils blood count as well as serum levels of creatinine and ferritin at the onset of DRESS syndrome could be useful prognostic factors

Patients and health care professionals, do you report side effects?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

#SideEffects #patientsafety

PHARMACOVIGILANCE

- The basis of pharmacovigilence is ADR reports submitted by clinician.
- The stakeholders involved are
- Clinicians,
- Pharmaceutical industries,
- Regulatory authorities &
- Patients.

Steps in pharmacovigilence

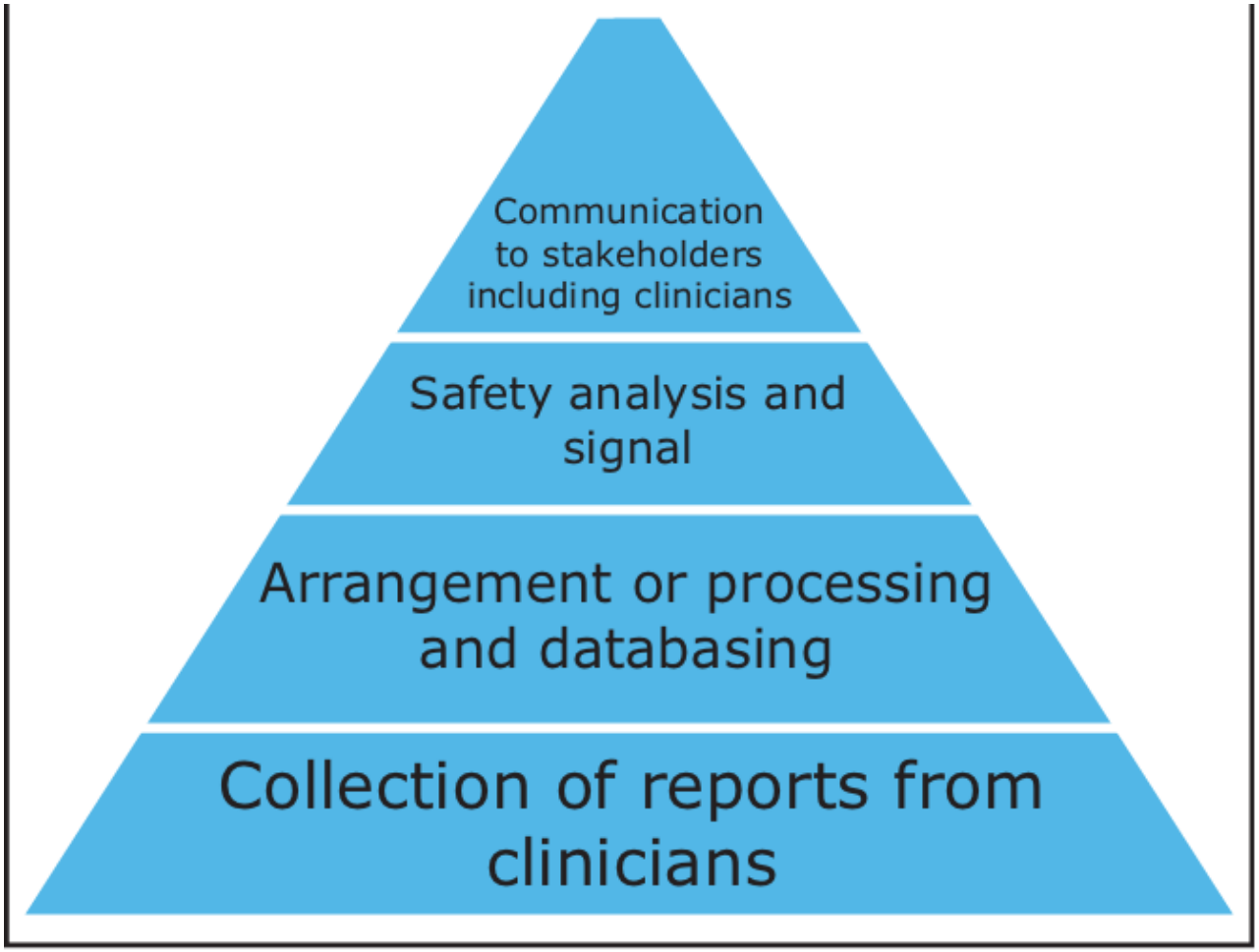


Fig. 50.1: Pyramid illustrating steps in pharmacovigilance.

Version-1.2

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by Healthcare Professionals

INDIAN PHARMACOPOEIA COMMISSION

(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare, Government of India
Sector-23, Raj Nagar, Ghaziabad-201002

Report Type ☐ Initial ☐ Follow up

A. PATIENT INFORMATION

1. Patient Initials _____

2. Age at time of Event or Date of Birth _____

3. M ☐ F ☐ Other ☐

4. Weight_____Kgs

B. SUSPECTED ADVERSE REACTION

5. Date of reaction started (dd/mm/yyyy)

6. Date of recovery (dd/mm/yyyy)

7. Describe reaction or problem

FOR AMC/NCC USE ONLY

AMC Report No. :

Worldwide Unique No. :

12. Relevant tests/ laboratory data with dates

13. Relevant medical/ medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction, etc.)

14. Seriousness of the reaction: No ☐ if Yes ☐ (please tick anyone)

- ☐ Death (dd/mm/yyyy)
- ☐ Life threatening
- ☐ Hospitalization/Prolonged
- ☐ Disability
- ☐ Congenital-anomaly
- ☐ Required intervention to prevent permanent impairment/damage
- ☐ Other (specify)

15. Outcomes

- ☐ Recovered
- ☐ Recovering
- ☐ Not recovered
- ☐ Fatal
- ☐ Recovered with sequelae
- ☐ Unknown

C. SUSPECTED MEDICATION(S)

S.No.	8. Name (Brand/Generic)	Manufacturer (if known)	Batch No. / Lot No.	Exp. Date (if known)	Dose used	Route used	Frequency (OD, BD etc.)	Therapy dates		Indication	Causality Assessment
								Date started	Date stopped		
i											
ii											
iii											
iv											

S.No. as per C	9. Action Taken (please tick)						10. Reaction reappeared after reintroduction (please tick)			
	Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Un-known	Yes	No	Effect unknown	Dose (if reintroduced)
i										
ii										
iii										
iv										

11. Concomitant medical product including self-medication and herbal remedies with therapy dates (Exclude those used to treat reaction)

S.No.	Name (Brand/Generic)	Dose used	Route used	Frequency (OD, BD, etc.)	Therapy dates		Indication
					Date started	Date stopped	
i							
ii							
iii							

Additional Information:

D. REPORTER DETAILS

16. Name and Professional Address:_____

_____

Pin:_____ E-mail:_____

Tel. No. (with STD code)_____

Occupation:_____ Signature:_____

17. Date of this report (dd/mm/yyyy):

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.

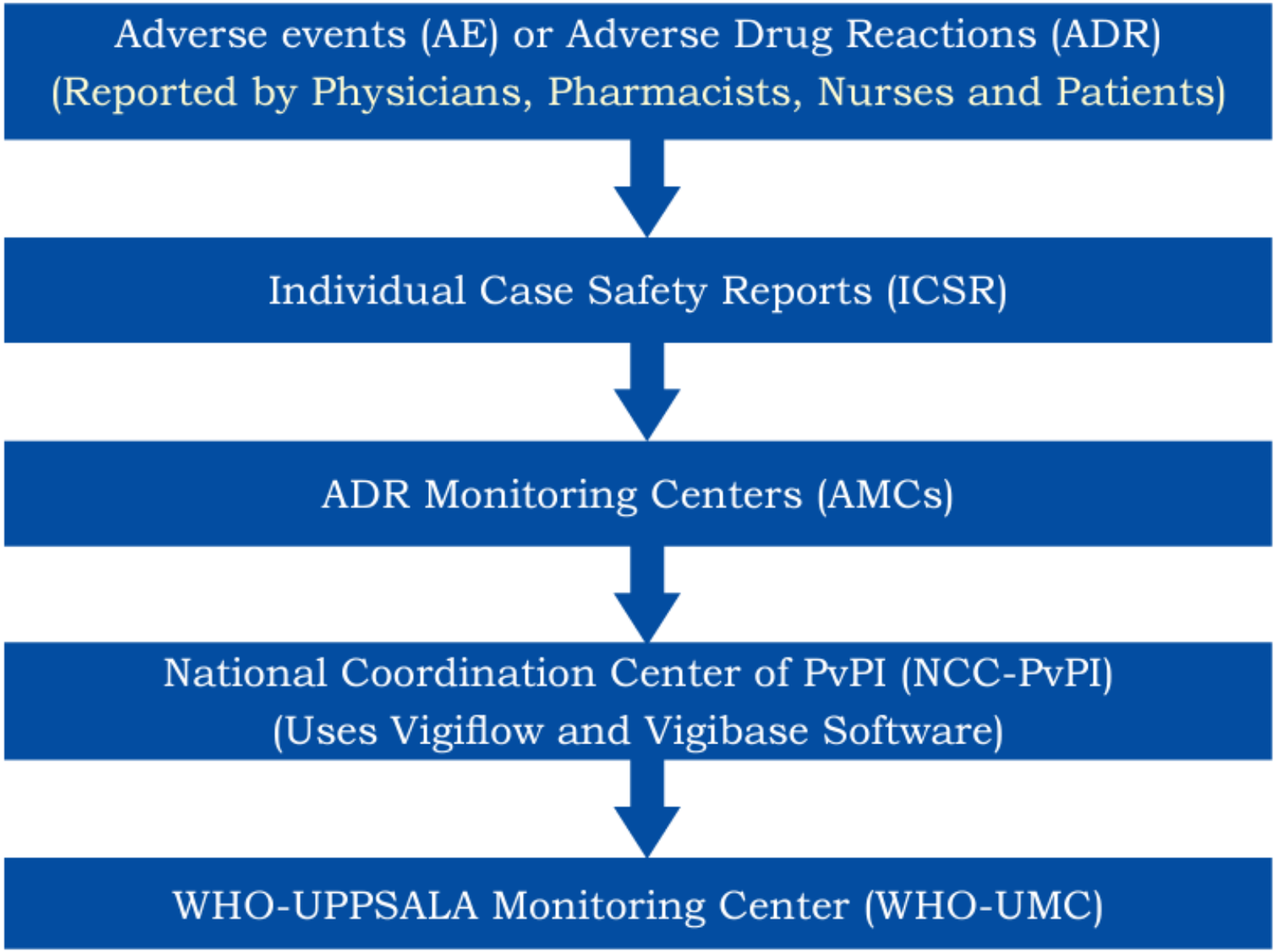


Fig. 1: Route map for reporting ADRs in India.

PvPI

- CDSCO in India initiated a nationwide pharmacovigilance programme in july 2010, with AIIMS, New delhi, as the National Coordination Centre(NCC).
- Later shifted to Indian Pharmacopenia Commission, Ghaziabad, UP in April 2011.

- Pvpi initiated a mobile app service - The " ADR reporting app" for android users.

For ADRs Reporting Call on PvPI Helpline (Toll Free)

1800 180 3024

(9:00 AM to 5:30 PM, Working Days)

TAKE HOME MESSAGE

- ADR can mimic almost any skin disease.
- Any drug can cause reaction in any person, any time. Family history is important.
- Antibiotics, analgesics & antiepileptics are responsible for > 75% of ADRs..
- Reporting ADRs to competent agency is important to ensure drug safety.

- A detailed history & good , thorough, methodical & meticulous clinical examination is necessary.
- Early recognition & withdrawal of offending or suspected drug is important.
- Avoiding suspected & chemically related drug is important to prevent recurrence.
- Rule out systemic involvement.
- We should be aware of

✓ Iatrogenic
✓ Idiosyncracy
✓ Intolerance
✓ Interactions&
✓ Idiopathic nature of the drugs


THANK
YOU