TOXIC TURN:
ESCALATED METHOTREXATE USE LEADING TO TOXICITY

PRESENTER : DR .M.KAUMUDI
(3RD YEAR PG)
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CHIEF COMPLAINTS

A 39 year old male patient who is a farmer by occupation hailing from Guntur presented with chief complaints of painful red colored raised lesions over scalp, trunk, both upper limbs , both lower limbs since 10 days

History of present illness :

Patient is a known case of psoriasis vulgaris from the past 8 years & using different medications intermittently. Patient is complaining of multiple red colored raised lesions present on scalp, trunk, both upper limbs and both lower limbs associated with pain and scaling.

- Lesions are increasing in size and number
- Patient had been consulting outside clinic and taking some unknown medications for 1 week and no subjective improvement seen.

- No H/O photosensitivity or joint pains
- No H/O weight loss
- No H/O target lesions
- No H/O fever prior to the onset of lesions

Past history

- Patient is a known case of psoriasis since 8 years and using different medications on and off .
- k/c/o DM , HTN .
- Not a k/c/o CAD/ TB /Asthma
- NO H/O drug allergies in the past

Treatment history :

- Patient is using Tab.METHOTREXATE irregularly. Up on further detailed history patient used Tab.METHOTREXATE 7.5mg od for 7 days and without taking folic acid supplementation.
- k/c/o Hypertension and using Tab amlodipine 5mg bd
- k/c/o DM and using Tab.Metformin 500mg bd

Family history

No h/o similar complaints in the family

No h/o any chronic illness in the family

Personal H/o

- Mixed diet
- Normal sleep and appetite
- Normal bowel and bladder
- Not a known smoker and not a known alcoholic

General examination

At the time of admission:

Patient is conscious, coherent and cooperative

No pallor/icterus/cyanosis/clubbing/lymphadenopathy/pedal edema

BP: 130/70mm of Hg

PR: 102/min

TEMP: 99 F

RR: 22/min

SPO2: 99% at RA

Cutaneous examination

- **ON EXAMINATION** : Multiple erythematous plaques , few plaques covered with loosely adherent silvery white scales present on B/L forearms ,elbows, B/L arms, lower abdomen , back of trunk, knees,anterior aspect of B/L legs , tenderness over lesions on both lower limbs present.
- **SCALP O/E** : Multiple hyperpigmented plaques covered with silvery white scales on vertex and occipital region.
- **Nails O/E** : Subungual hyperkeratosis noted in great toe and 2nd toe of B/L feet. Deep irregular pitting present over B/L fingernails.

- ORAL MUCOSA : NAD
- OCULAR MUCOSA :NAD
- GENITAL MUCOSA. :NAD

SYSTEMIC EXAMINATION

- CVS : S1 AND S2 Heard ,no added sounds
- RS :B/L Normal vesicular breath sounds heard, no adventitious sounds
- GIT : Per abdomen : soft ,no organomegaly
- CNS : NAD

- **PROVISIONAL DIAGNOSIS :**

- PSORIASIS VULGARIS

- **Base line investigations :**
- CBP
- LFT
- RFT
- RBS

ON DAY 1

Patient was started on

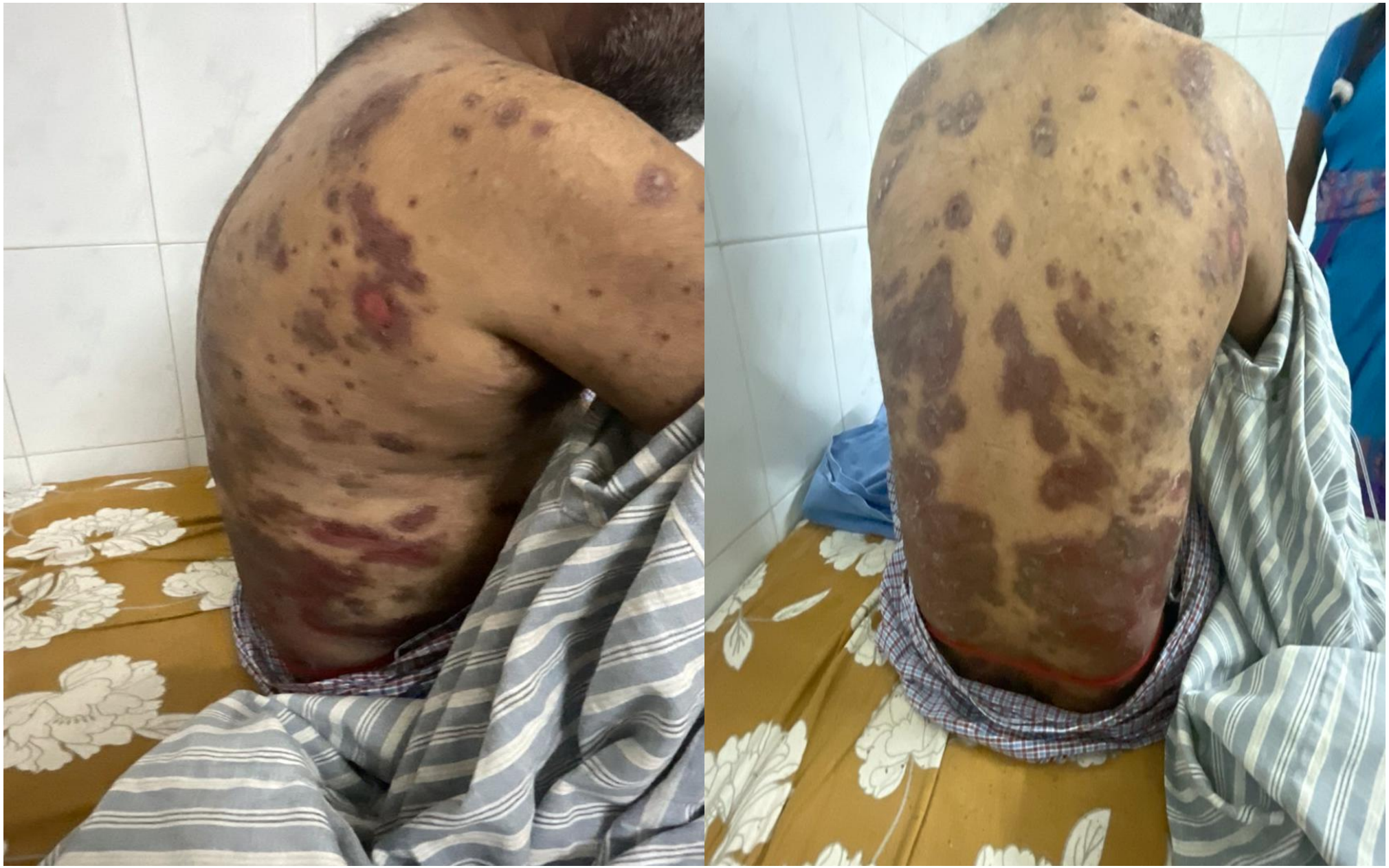
- Tab APREZO(APREMILAST)10mg (starter pack)
- PROPYSALIC LOTION (E/A over lesion on scalp twice daily)
- SALYTAR SHAMPOO(E/U for head bath twice weekly)
- LIQUID PARAFFIN (E/A over body)
- Supportive management
- Tab LEVOCETRIZINE 5mg OD
- Tab SHELCAL 100 mg OD
- Tab PARACETAMOL 650 mg sos
- Tab AMLODIPINE 5mg BD
- Tab METFORMIN 500mg BD

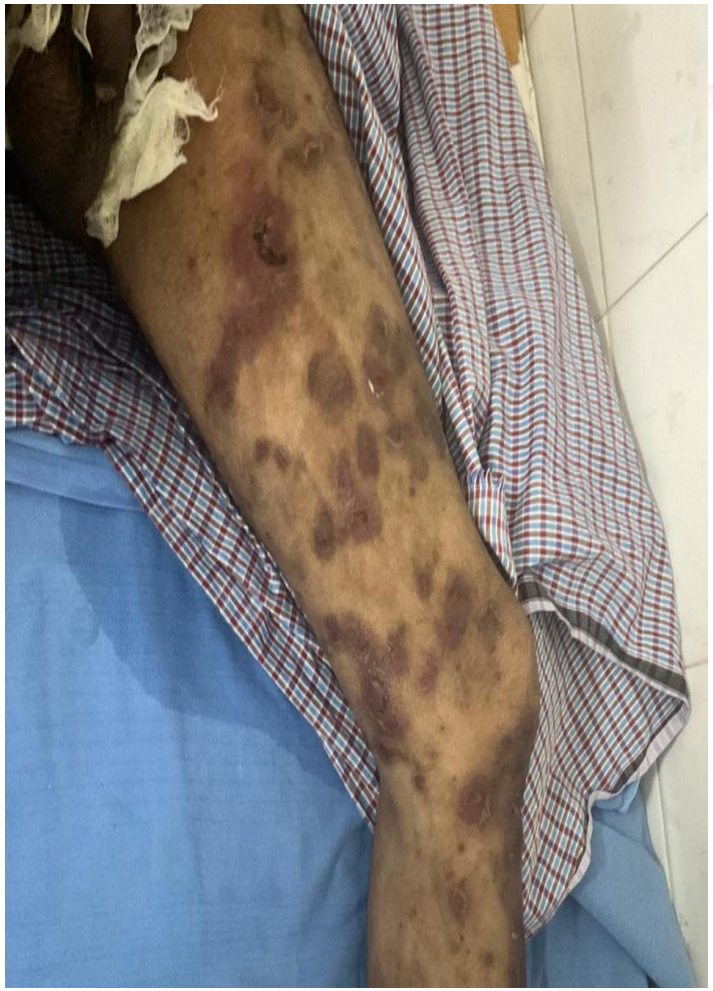
ON DAY 2

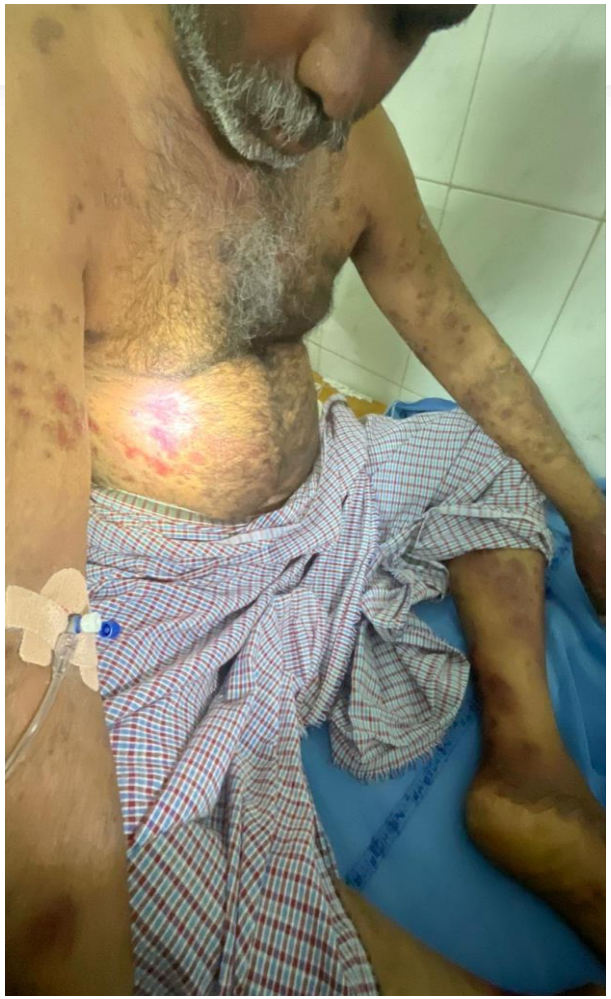
- Patient complaints 2 episodes of vomiting and 6 episodes of diarrhoea
- c/o body pains
- c/o painful lesions over both groins
- And temperature was 99.7degree F
- We added
- Tab PARACETAMOL 650 mg BD
- Tab SPOROLAC DS TID
- Tab ONDANSETRON 4mg TID
- Tab PANTOP 40mg
- INJ H Actrapid s.c 8 th hourly according to sliding scale

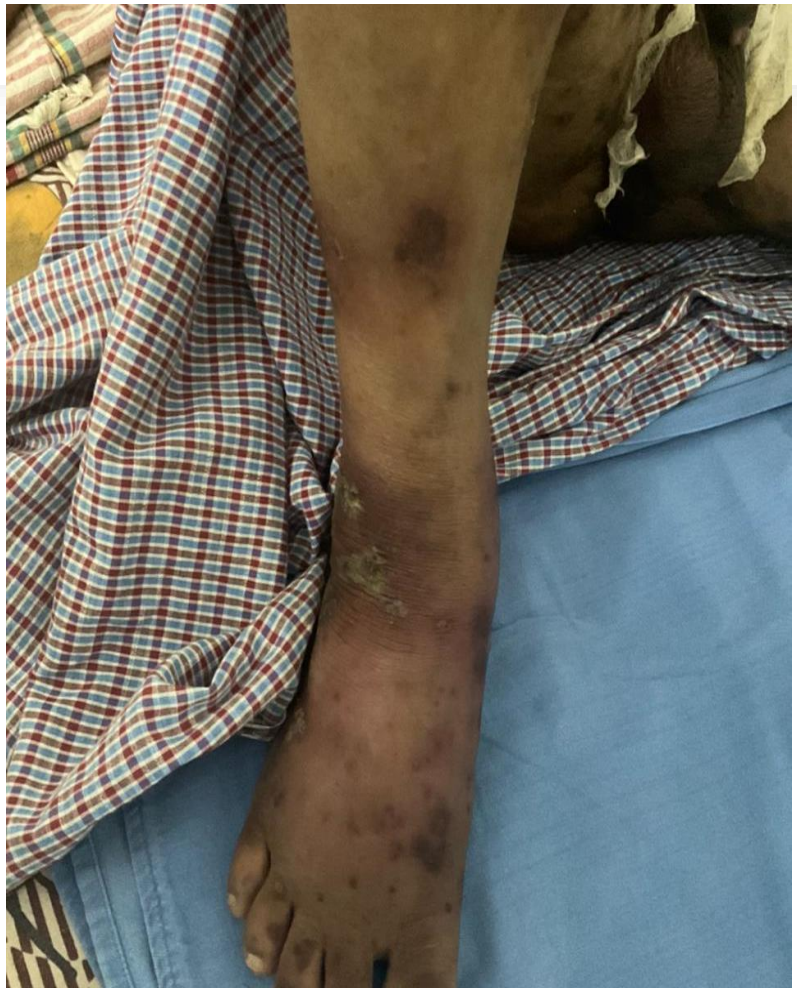
ON DAY 3

- c/o 3 episodes of diarrhoea
- c/o burning micturition
- c/o painful lesions present in mouth
- c/o dysphagia present
- **on examination** : Small ulcers developed around the margins of the existing lesions in the lower limbs and front and back of trunk . Erythema and swelling present in dorsum of both hands and both feet.
- **Oral cavity O/E**: multiple erosions present in B/L buccal mucosa and hard palate









date	DAY 1	DAY 2	DAY 3	
HB	12.8	10.8	10.3	
TOT COUNT	4800	3780	2100	
NEUTROPHIL COUNT	73%	71%	42%	
ESR	50	60	70	
PLATELET COUNT	3.2Lakhs/mm3	2.3Lakhs/mm3	1.5Lakhs/mm3	

LFT	DAY 1	DAY 3	RFT	DAY 1	
Tot bil	1.6	2.0	Sr CREATININE	1.1	
Indirect bil	1.0	1.1	Sr UREA	52	
Direct bil	0.6	0.9	Sr NA	N	
Ast	N	N	Sr K	N	
Alt	N	N	Sr cl	N	
Alk pos	N	N			
Sr albumin	3.2 LOW	3.1			

- considering the laboratory findings and clinical features , diagnosed it as methotrexate toxicity .
- Patient is advised to discontinue Tab.METHOTREXATE.
- General medicine and medical oncology referral/opinion. Patient was started on

- INJ.LEUCOVORIN 15 mg i.v qid in 100 ml NS 6 th hourly
- CONTINOUS I.V FLUIDS NS and RL 125ml/hr ALONG WITH INJ.NaHCO3 10cc
- INJ.PIPTAZ 4.5gm in 100ml NS TID
- INJ H ACTRAPID S.C 8 TH hourly
- INJ.LASIX 20 MG STAT
- Tab FOLVITE 5 mg od
- Syp CITRALKA 10 ml tid

- On day 4 the HB :9.1 gm/dl ,

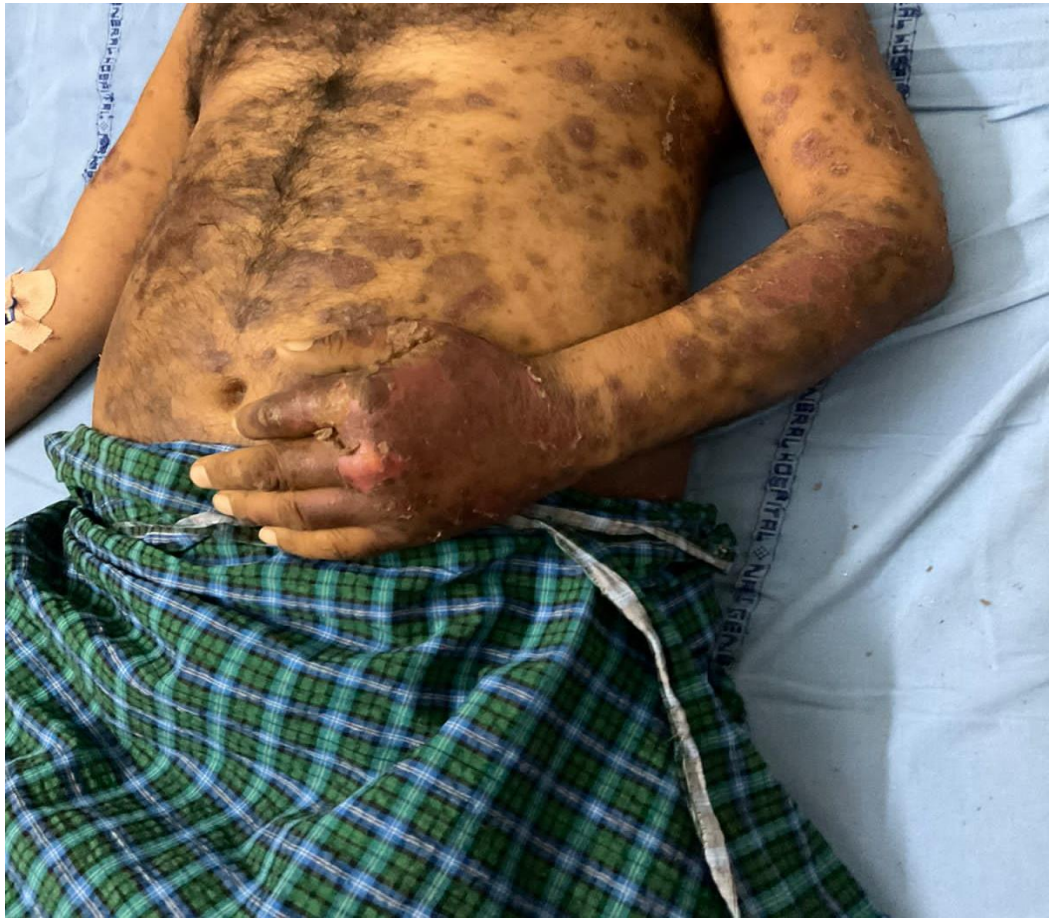
  Tc:2700 and

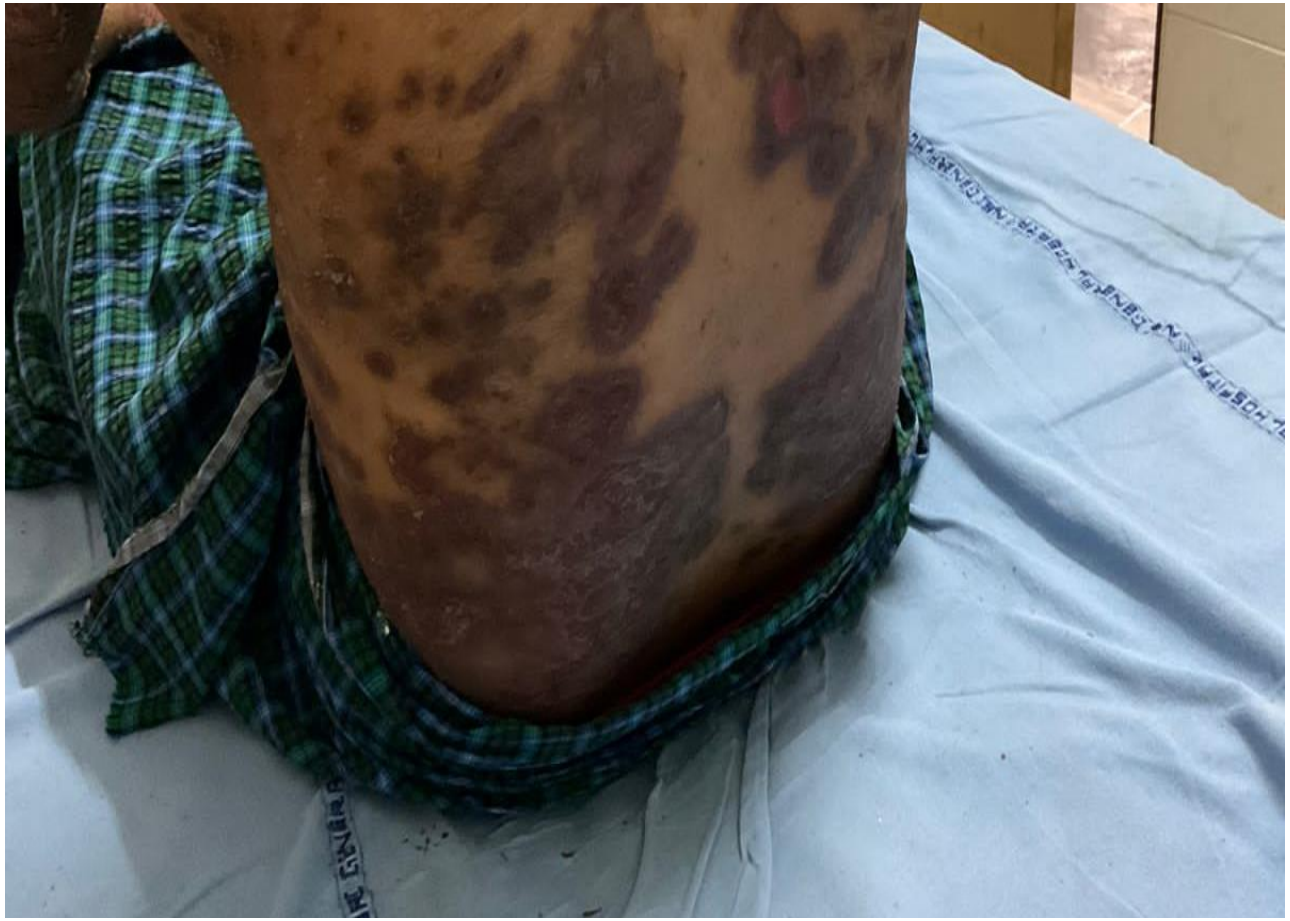
  PC:1.5Lakhs/mm3

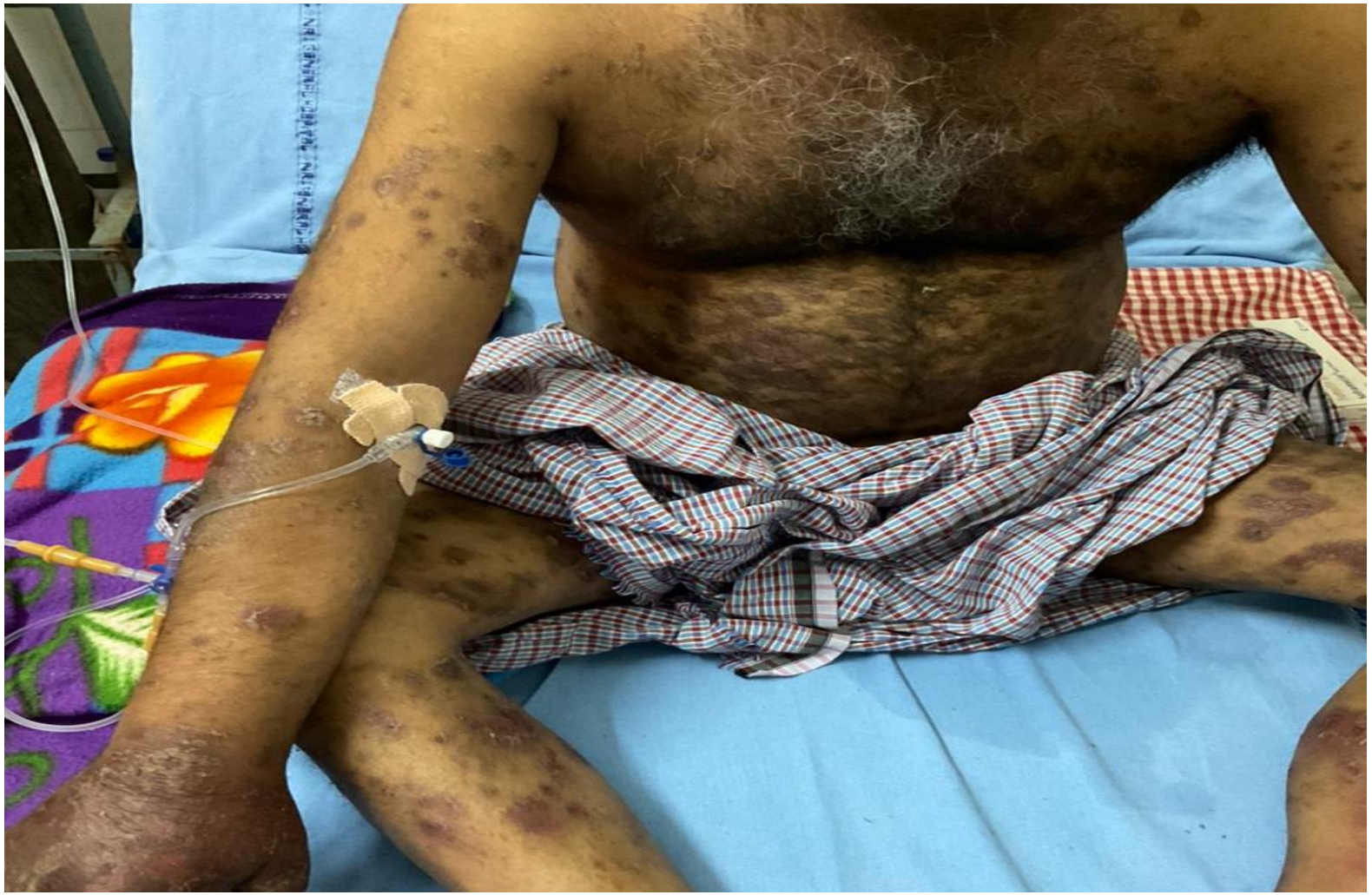
- INJ NEUKINE (G-CSF) 300mcg given Subcutaneous stat .

- DAY 5 the HB : 8.9 gm/dl
- TWbc : 5000
- PC : 1.6Lakhs/mm3
- INJ Leucovorin 15mg I.V QID
- Patient clo 5 episodes of diarrhea and nausea which can be the side effect of apremilast and we stopped tab aprezo

Day 5







- **ON DAY 8:**
- Skin lesions and lab counts are improving .so, INJ LEUCOVORIN along with I.v fluids was stopped
- Rest of the treatment is continued

INVESTIGATIONS

CBP	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	DAY 8	
HB mg/dl	12.8	10.8	10.3	9.1	8.9	9.4	9.9	10.7	
WBC TOT Mill/cum	4800	3780	2100	2770	5000	4000	4100	5400	
PLAT CT	3.2L	2.3L	1.5L	1.5L	1.6L	1.2L	1.1L	3.7L	

RFT	DAY 1	DAY 4	DAY 5	DAY 6	DAY 8	
S.CREATININE	1.1	0.8	0.9	0.8	0.9	
BLOOD UREA	52	17	27	12	22	
S.NA	N	N	N	N	N	
S.K	N	N	N	N	N	
S.CL	N	N	N	N	N	

Investigations

- Chest x ray
- ECG
- CUE
- USG ABDOMEN
- BLOOD CULTURE
- LIPID PROFILE

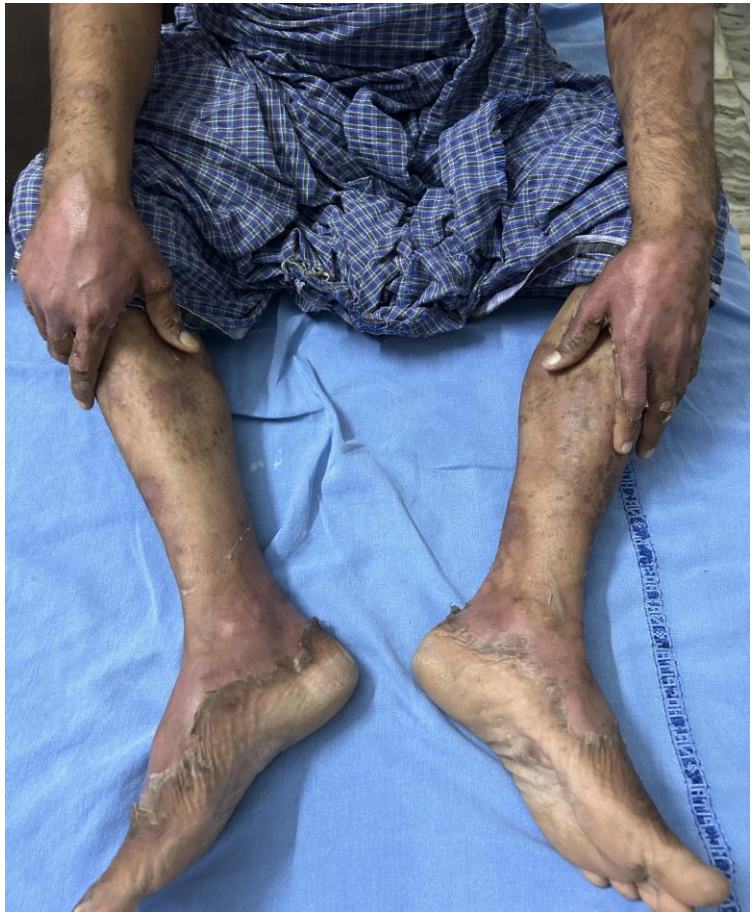
TREATMENT DURING HOSPITAL STAY

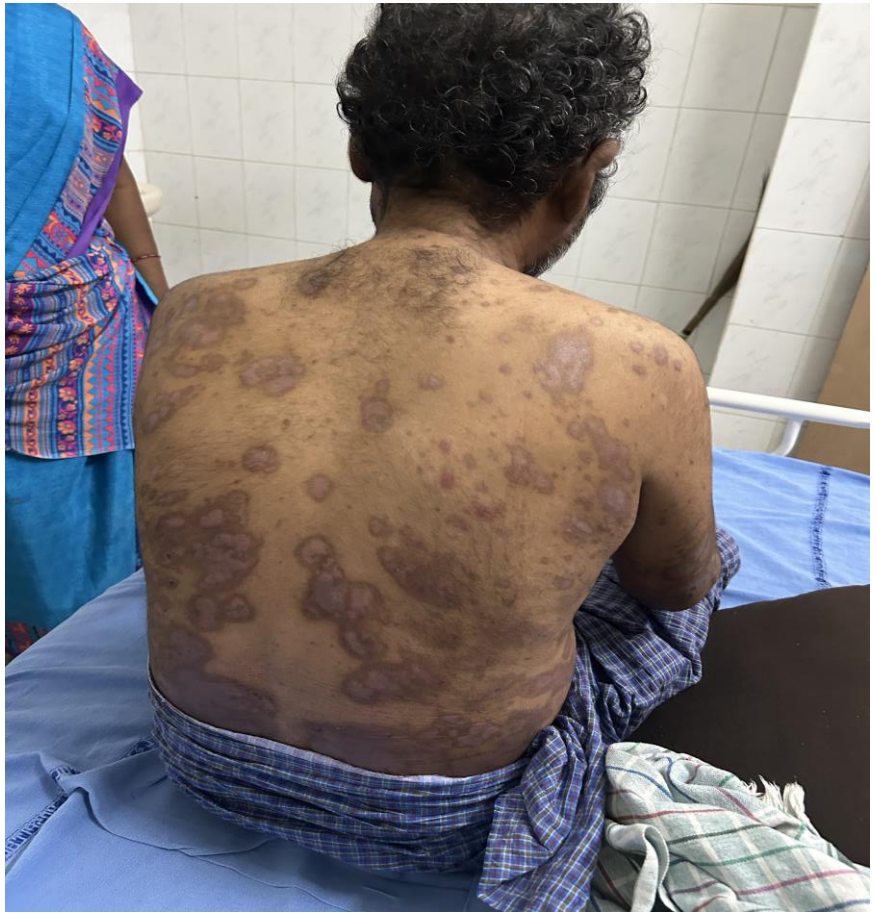
1) INJ LEUCOVORIN 15 mg i.v qid in 100 ml NS 6 th hourly for 6 days
2) INJ PIPTAZ 4.5gm in 100ml NS TID for 6 days
3) CONTINOUS I.V FLUIDS NS ALONG WITH INJ.NAHCO3 10cc .
4) INJ H ACTRAPID S.C 8 TH hourly according to sliding scale
5) INJ LASIX 20 MG STAT
6) INJ NEUKINE (G-CSF) 300 mcg s/c stat
7) TAB APREZO starter pack
8) Tab FOLVITE 5mg OD
9) Tab LEVOCETRIZINE 5mg OD

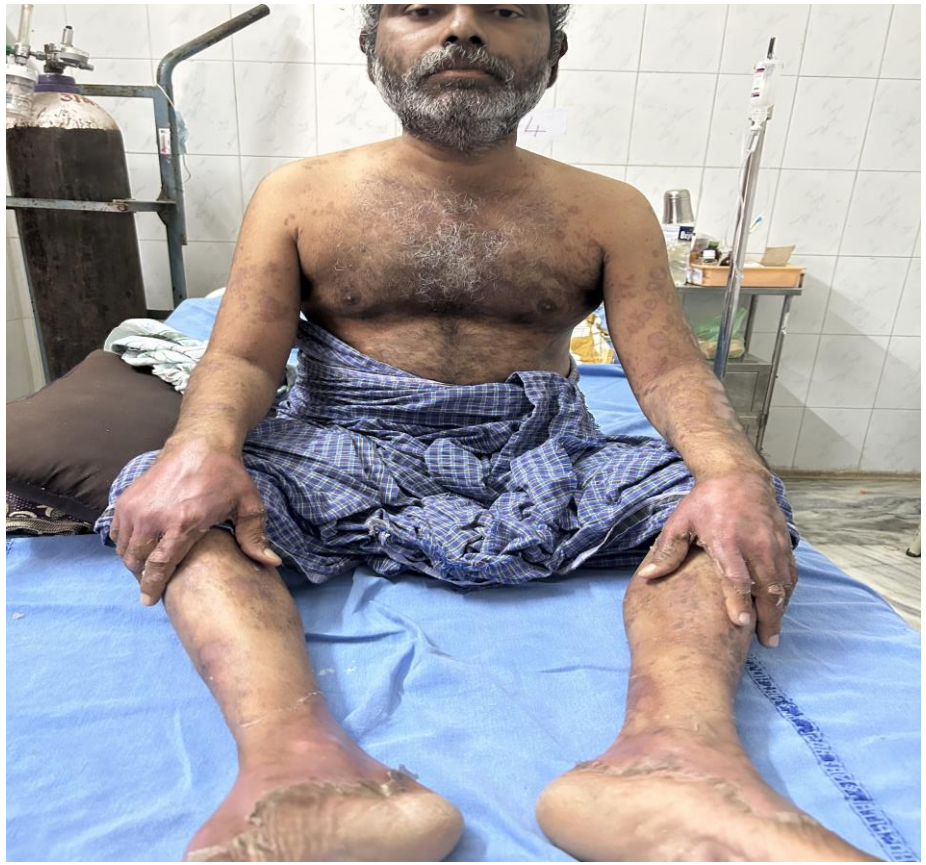
SUPPORTIVE TREATMENT

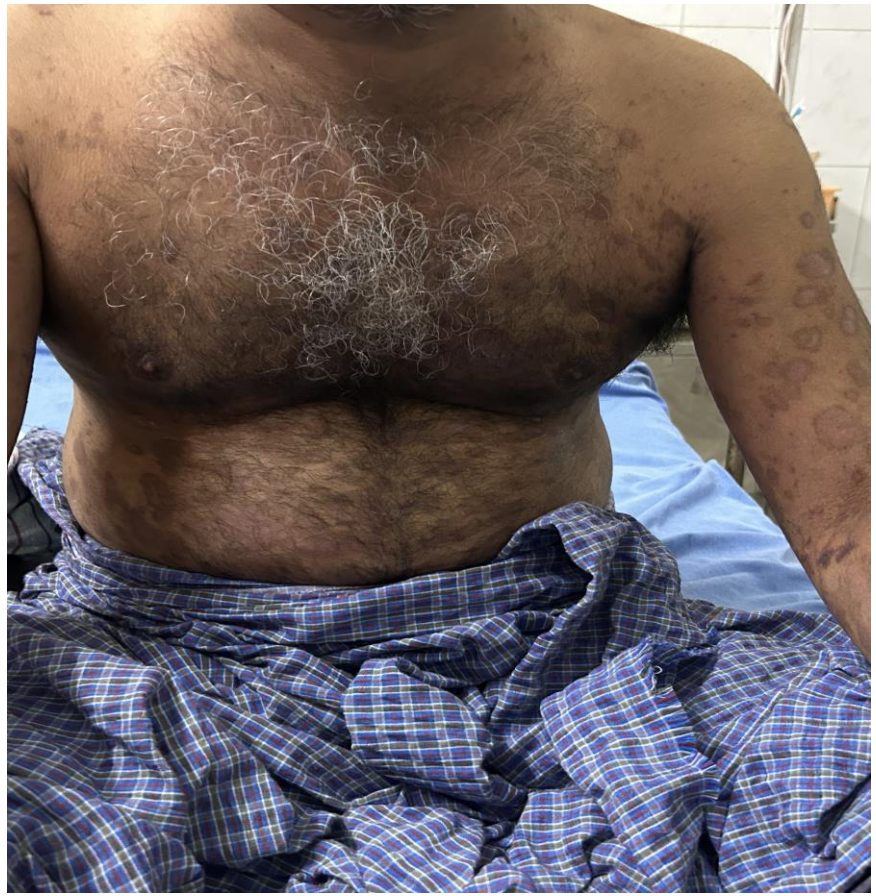
1. Tab. SHELCAL 500mg OD
2. Tab. AMLODIPINE 5mg BD
3. Tab . PANTOP 40 mg OD
4. MUCOPAIN gel (E/A in oral cavity)
5. SOFRAMYCIN cream (E/A over erosions)
6. Syrup MUCAIN 15 ml TID
7. Saline compressors over crusts TID

At the time of discharge





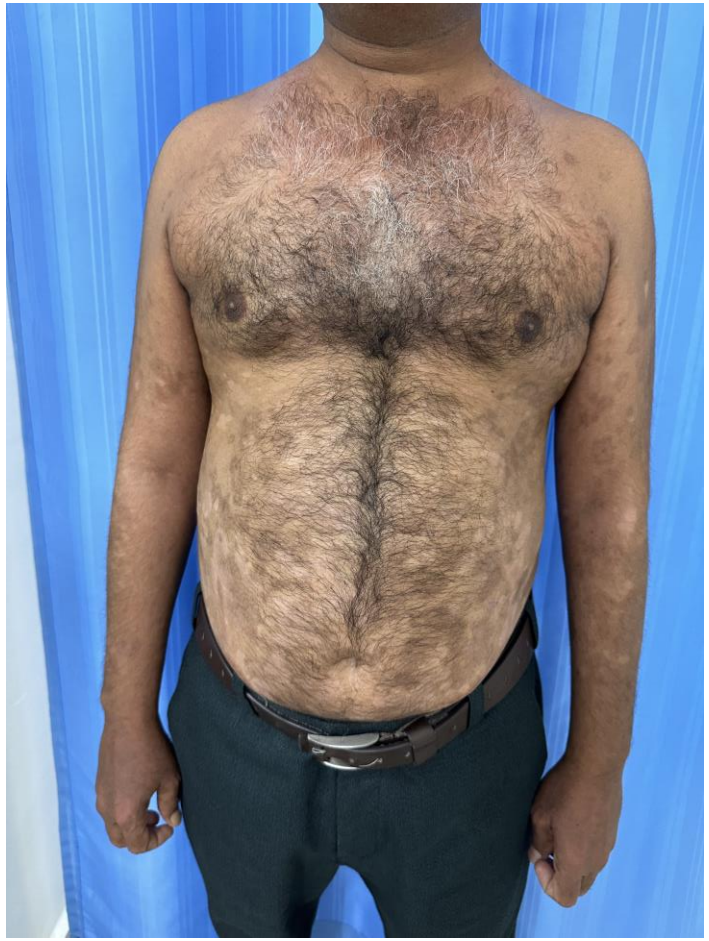


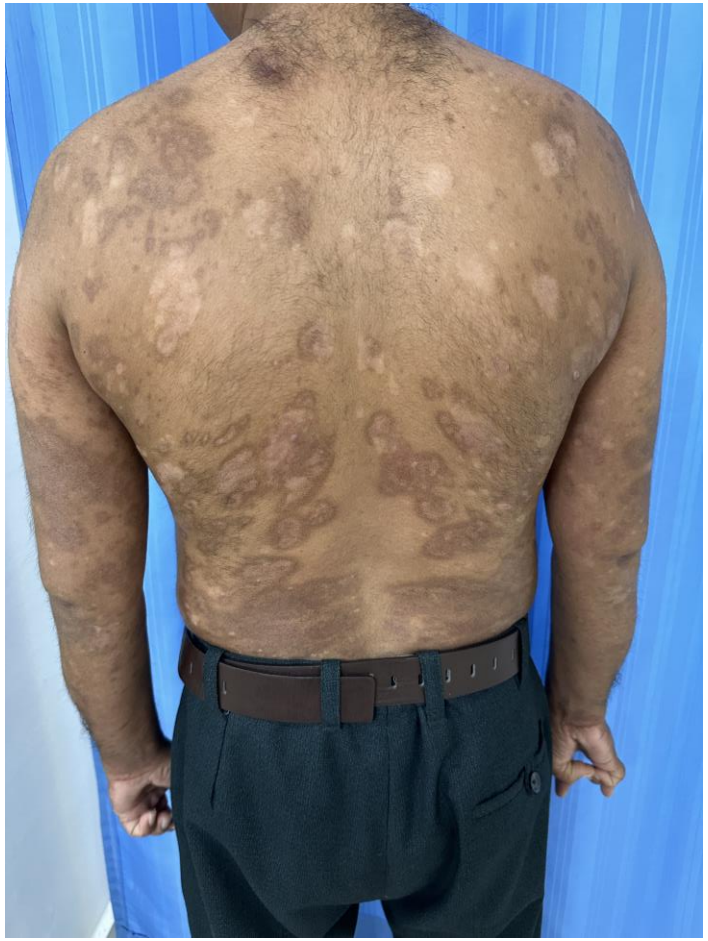


Discharge medications

- Cap CYCLOSPORINE 100mg morning and 50 mg night time
- Tab LEVOCETRIZINE 5mg od
- Tab SHELCAL 500mg od
- LIQUID PARAFFIN (E/A over body twice daily)
- PROPYSALIC NF 6 lotion (E/A over lesions over scalp)
- SALYTAR SHAMPOO(E/U for head bath)

1 month follow up





Methotrexate toxicity

- Methotrexate is a synthetic analog of folate that competitively and irreversibly inhibits DHF reductase ,therefore inhibits folic acid metabolism acting as anti-inflammatory and immunosuppressant and immunomodulation action in low doses
- Elimination is mainly by kidneys
- 60% - 95% excreted unchanged
- 50% MTX is protein bound
- Oncological doses : 100- 200mg/m2/week
- In Dermatological doses : 7.5 – 25 mg/wk

Clinical features

- **Mucosal and cutaneous effects**
- oral ulceration and stomatitis .
- Rapid ulceration of the psoriatic plaques particularly in the lower limbs herald to bone marrow suppression and indicates methotrexate toxicity .
- Mild alopecia .
- Other cutaneous manifestations : acral erythema , epidermal necrosis , vasculitis .

- **GI SIDE EFFECTS**
- Nausea and vomiting are usually dose related
- Supplementation with FOLVITE 1- 5 mg/day reduces GI side effects

- **HEMATOLOGICAL SIDE EFFECTS**
- Acute side effects includes myelosuppression
- Neutropenia if present life threatening
- **Risk factors**
- Advanced age
- Poor renal function
- Hypoalbuminemia
- Lack of FOLVITE supplementations
- Concurrent administration of drugs

- **HEPATIC SIDE EFFECTS**
- Hepatotoxicity and hepatic fibrosis are long term side effects
- Liver transaminases are elevated ,monitor 5-6 days after last dose
- Dose reduction is indicated if transaminases increases 2-5-fold
- Discontinue if increase to 5 fold

- **PULMONARY SIDE EFFECTS**
- Acute pneumonitis and pulmonary fibrosis m.c in RA patients
- Pulmonary toxicity – idiosyncratic reaction
- **Strong prediction**
- Old age
- Dm
- Rheumatoid pleuro pulmonary involvement
- Hypoalbuminemia
- Previous use of DMARDS

- **INVESTIGATIONS**
- COMPLETE BLOOD PICTURE
- LIVER FUNCTION TESTS
- RENAL FUNCTION TEST
- SERUM ASSAY OF METHOTREXATE LEVELS
- NON INVASVE BIOMARKERS : SERUM PRO COLLAGEN 3 AMINOTERMINAL PEPTIDE
- ESR

- **Absolute contraindications**
- Pregnancy (category X) ,Lactation
- Significant anaemia, leukopenia, or thrombocytopenia
- **Relative contraindications**
- Renal dysfunction (dose may be reduced)
- Hematologic disease (dose may be reduced)
- Hepatic disease or hepatic dysfunction
- Unreliable patient
- Excessive alcohol consumption
- Diabetes mellitus and/or obesity
- Active infection and/or potential reactivation of infection (tuberculosis)
- HIV infection
- Man or woman contemplating impending conception

Drug interactions

- Aspirin
- NSAIDS
- Probenecid
- Sulfonamides ,aminoglycosides
- Penicillins ,minocycline ,ciprofloxacin
- Phenytoin , barbiturates
- Sulphonylureas
- Trimethoprim sulphamethoxazole
- Colchicin

MANAGEMENT

- The mainstay of treatment is folinic acid (leucovorin) , start with in 24 to 36 hrs after overdose
- Oral dose -10mg/m^2 or 15 to 25 mg every 6 hours for 6 to 10 doses without any delay for serum assay.
- If serum assay is available , oral or parenteral doses continue every 6hrs until serum concentration of Methotrexate fall to less than 0.2 micro moles/litre
- Prophylactic systemic antibiotics
- Tab.FOLVITE 5MG OD DAILY

Supportive management

- Continuous fluid management with NaHCO3
- Topical antiseptics
- Topical emollients
- Tab.fluconazole 150 mg od
- Syrup mucain 15 ml Tid
- Saline compressors TID

References

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- Rook's textbook of dermatology 9th edition
- Fitzpatrick's textbook of dermatology 9th edition
- Montaudie H, Sbidian E, Paul C, Maza A, Gallini A, Aractingi S et al. Methotrexate in psoriasis: a systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity. J Eur Acad Dermatol Venereol. 2021; 25(2):12-8.

THANK YOU