

Cutaneous Manifestations of Connective Tissue Diseases: A Clinical Study

Dr. N. Thasleem Begum¹, Dr.Y.Aruna Kumari M.D², Dr.I.Chandrasekhar Reddy M.D., D.D³

¹Post Graduate, ²Associate Professor, ³Professor and HOD, Department of Dermatology, Kurnool Medical college, Kurnool -518002, Dr NTR University of Health and Sciences, Vijayawada, Andhra Pradesh, India.

Corresponding Author: Dr.Y.Aruna Kumari M.D., Associate Professor of Dermatology, Flat No. 203, A Block, S.V. Pride Apartments, Birla compound, Gootty Road, Kurnool -518002, Andhra Pradesh, India.

Abstract

Background: Connective tissue diseases are a group of disorders with inflammatory and immunological changes in connective tissues and blood vessels. They present with various cutaneous manifestations.

Objective: The study was conducted to know various cutaneous manifestations of connective tissue diseases.

Materials and methods: This prospective/longitudinal study conducted in 40 patients of clinically diagnosed connective tissue diseases in a tertiary care hospital during a period of one year from March 2018 to 2019. Cutaneous LE, Systemic sclerosis, Dermatomyositis and MCTD were included in study. Drug induced cases were excluded. History, detailed cutaneous examination, investigations was done in all patients. Cutaneous features were enumerated.

Results: In the present study, LE was present in 25 cases(62.5%) , Systemic sclerosis in 10(25%) , Dermatomyositis in 3(7.5%) and MCTD in 2 (5%). Majority were females (77.5%) . Most of them were in age group of 31-40years. Among LE cases, CCLE were common (36%). Photosensitivity(48%) and Malar rash(44%) were common. Renal involvement (20%) was common in SLE. Sclerosis of skin(100%) was most common in systemic sclerosis.

Conclusions: Female preponderance seen in our study. Most of CTDs were in 31-40 years. LE was the commonest CTD.

Keywords: Connective tissue diseases, Dermatomyositis, Lupus erythematosus, MCTD, Systemic sclerosis.

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I. Introduction

Connective tissue diseases are a group of multisystem clinical disorders that have autoimmune pathogenesis which cause chronic inflammation leading to injury and destruction of tissue(1) . Autoantibodies target collagen and elastin which are found in almost every organ of body. These collagen and elastin provide support and stretching of connective tissue and skin. Systemic involvement in connective tissue diseases is often unclear and organ changes are confounding , thus making it difficult to have an early accurate diagnosis. Hence, skin findings on physical examination can give critical clues for the diagnosis of many CTDs and certain signs often represent the early stage of disease by its presenting symptoms. Therefore comprehensive knowledge of cutaneous manifestations is essential for accurate early diagnosis and alert the clinicians for early intervention and effective management of localised cutaneous abnormalities that result in cosmetic deformities and other debilitating systemic complications. This inspired us to study the various cutaneous manifestations of certain important CTDs that include Systemic lupus erythematosus, Scleroderma (Systemic sclerosis) , Dermatomyositis and Mixed connective tissue disease in Tertiary care hospital of Rayalaseema region of South India.

OBJECTIVE: To study various cutaneous manifestations of connective tissue diseases.

II. Materials and Methods

This is a Prospective / longitudinal study undertaken in the department of DVL at a Tertiary care hospital attached to Medical college. The study was conducted during a period of one year from March 2018 to March 2019. Total of 40 patients who presented with cutaneous manifestations of CTDs like Cutaneous LE, Systemic sclerosis, Dermatomyositis and MCTD were included in the study. Drug induced cases were excluded.

After taking informed consent, demographic data was collected. All the patients were evaluated for cutaneous manifestations of SLE, both specific and non specific. For Systemic sclerosis ,ACR 1980 criteria based on the nature and extent of skin involvement (typical skin thickening and hardening) along with presence of auto antibodies and with certain organ involvement was used. For MCTD, Alarcon-Segovia criteria was used with presence of 3 clinical features among edema of hands ,acroscerosis, raynauds phenomenon,synovitis,myositis and serological positivity of U1 RNP with desirable titre.

III. Results

Total 40 patients with CTDs who fulfil the criteria were included in the present study. Among them Lupus erythematosus were 25(62.5%) , 10 (25%) were systemic sclerosis, 3 (7.5%) patients with Dermatomyosistis and 2 (5%) patients with MCTD were present (Figure 1). Total of 31 (77.5%) female patients,out of 40 cases in our study indicates female preponderance. Total of 17 (42.5%) patients were in the age group of 31-40 years (Figure 3). Youngest age in our study was 5 years old and eldest was 62 years old.

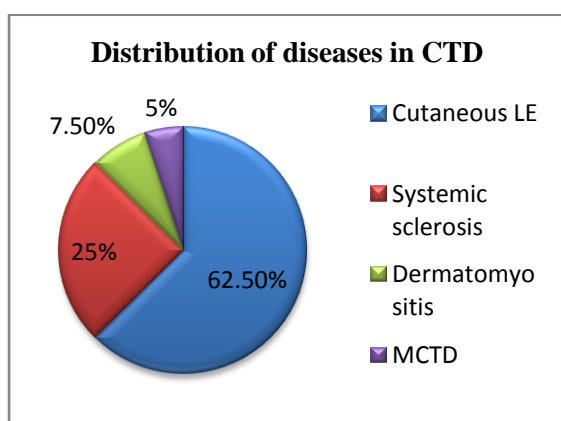


Figure 1: Dia. of disease distribution

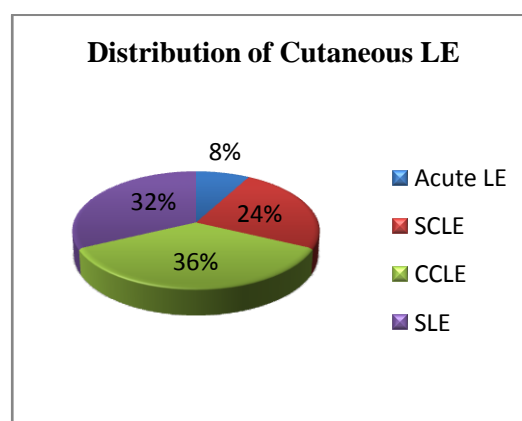


Figure 2: Dia. of Cutaneous LE distribution

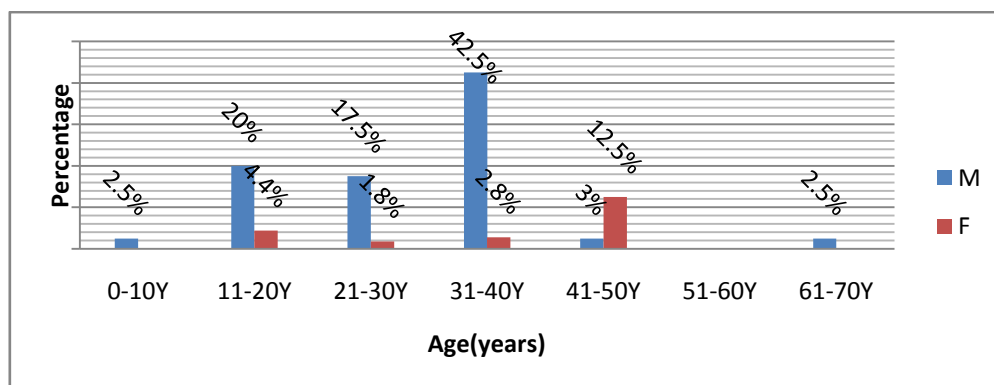


Figure 3: Dia. of age and sex wise distribution

Out of total 25 patients of Lupus erythematosus in the present study. 2 (8%) presented with Acute LE, 6 (24%) were Subacute cutaneous LE , 9 (36%) were Chronic cutaneous LE and 8 (32%) patients presented with systemic involvement(Figure 2). Out of 25 LE patients,19 (76%)were females and 6(24%) were males. Youngest age was 11 years old and eldest was 50 years old. Mean age ± standard deviation was 30.24 ± 10.33.LE specific skin lesions like Malar rash present in 11(44%) patients, Papulosquamous rash present in 6(24%), Discoid rash in 8 (32%) and LE profundus in 1 (4%) patient. LE non specific features like Photosensitivity seen in 23(92%)patients , Oral ulcers in 8(32%), raynauds phenomenon in 7 (28%), Non scarring alopecia in 5 (20%) and vasculitis in 2 (8%) patients respectively (Table 1).

Table No.1 : Specific and Non specific features of LE

Features of LE	Number of Males	Number of females	Total	Percentage
Malar rash	0	11	11	44%
Papulosquamous rash	1	5	6	24%

Discoïd rash	2	6	8	32%
LE profundus	0	1	1	4%
Photosensitivity	1	11	12	48%
Oral ulcers	1	7	8	32%
Raynauds phenomenon	0	7	7	28%
Non scarring alopecia	0	5	5	20%
Vasculitis	1	1	2	8%
Total	8	17	25	100%

Among 8 (32%) cases of SLE, Neurological involvement was present in 3 (12%) patients and renal involvement present in 5 (20%) patients. Among 5 patients with renal involvement, 1 patient with biopsy proven Diffuse Proliferative Glomerulonephritis (DPGN) and remaining were presented with hypoalbuminemia, proteinuria, hypertension. Among 40 cases of CTDs, 10 (25%) patients fulfil the ACR (1980) criteria for systemic sclerosis. Out of these 8 (80%) were Limited SSc and 2 (20%) were Diffuse SSc. 9 (90%) patients were females and 1 (10%) was male. Youngest was 20 years old and eldest was 50 years. Cutaneous manifestations like skin tightening was present in all 10 (100%) patients, salt and pepper dyspigmentation present in 9 (90%), raynauds phenomenon present in 8 (80%), digital tip ulcers present in 5 (50%), radial furrowing in 4 (40%) patients, digital pits in 3 (30%) patients, parrot beak nose present in 3 (30%), decreased forehead wrinkling was seen in 3 (30%) and 2 (20%) show bulbous fingers (Table 2).

Table No.2 : Cutaneous manifestations of Systemic sclerosis

Symptoms	Skin tightening	Salt & pepper pigmentation	Raynauds phenomenon	Bulbous fingers	Digital pits & ulcers	Decreased Forehead wrinkling	Radial furrowing	Parrot Beak nose
No. of patients	10	9	8	2	8	3	4	3
Percentage	100%	90%	80%	20%	80%	30%	40%	30%

One male patient presented with skin tightening, salt and pepper pigmentation, raynauds phenomenon, digital tip ulcers and GI involvement. Dermatomyositis was present in 3 (7.5%) patients, among them 2 were males and 1 was female. MCTD was present in 2 (5%) cases and both were females.

IV. Discussion

Autoimmune connective tissue diseases represent polygenic clinical disorders that have heterogenous and overlapping clinical features. They are characterised by an immune dysregulation involving production of auto antibodies to self antigens. These are multisystem diseases presenting with involvement of skin and mucous membrane¹.

Cutaneous lupus erythematosus, Scleroderma, Dermatomyositis are CTDs with significant cutaneous manifestations that may exhibit widespread systemic manifestations but varied presentation of clinical spectrum in each entity makes classification of CTDs difficult and challenging to the clinician especially in case of Overlap/Undifferentiated connective tissue disorders.

The term "Lupus erythemateux" was introduced by Alphee Cazenave in 1857. Involvement of various organ systems was described and "Organ lupus" was distinguished from "Skin lupus". Marrack, Kappler and Kotzin have proposed that the genetic and environmental factors lead to autoimmunity. James N Gilliam based on histological criteria, distinguished the cutaneous manifestations into LE specific skin disease and LE non specific skin disease². (Table 3 and 4).

Table No.3: Specific LE skin lesions

1. Acute cutaneous lupus erythematosus Localized form & Generalized form	3. Chronic cutaneous lupus erythematosus a. Discoïd lupus erythematosus Localized form & Generalized form b. Lupus erythematosus profundus c. Chilblain LE
2. Subacute cutaneous lupus erythematosus Annular form Papulosquamous form	4. Intermittent cutaneous LE LE Tumidus

Table No.4 : Non Specific LE skin lesions

1.Leucocytoclastic Vasculitis Palpable purpura Urticarial vasculitis 2.Livedo racemosa 3.Thrombophlebitis 4.Occlusive vasculopathy	5.Raynauds syndrome 6.Periungual telangiectasia 7.Diffuse non scarring alopecia 8.Calcinosis cutis 9.Papular mucinosis 10.Erythema Multiforme
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Scleroderma includes both localised forms and systemic forms that manifest internal organ features as well as demonstrating vascular manifestations. Systemic sclerosis is a multisystem autoimmune disease with incidence of 1/100000. Clinical manifestations ranging from mild skin fibrosis with minimal internal organ disease to severe skin and organ involvement with associated vascular and inflammatory manifestations including raynauds phenomenon . Immune abnormalities or autoimmune dysregulation , endothelial damage inturn cause fibroproliferative alterations leading to excessive fibrosis³.

Systemic sclerosis presents with raynauds phenomenon, thickening and fibrosis of skin mostly over extremities and face in limited forms of SSc and much more extensively in diffuse cases. Associated features include telangiectasia,calcinosis,diffuse hyperpigmentation and salt and pepper dyspigmentation.The most common systemic complication involves the Gastrointestinal tract which can lead to altered motility , bacterial overgrowth and malabsorption. Diffuse SSc can also present with fibrosis in other visceral organs such as Lung (30%), Heart (10%) and kidney (12%)⁴.

Dermatomyositis (DM) is an autoimmune disorder which affects skin and skeletal muscle predominantly. Dermatomyositis and polymyositis combined have incidence and prevalence rates of 1 to 10 and 10 to 60 cases per million population respectively⁵. Skin manifestations occur in approximately 70% of patients include Gottron’s papules , periungual telangiectasia, erythematous lilac heliotrope macular rash and periorbital edema involving the eyelids and erythematous, poikilodermatous macules in a shawl like distribution over the shoulders, arms, and upper back(Shawl sign) and cutaneous vasculitis. Muscular involvement in DM/PM includes symmetrical weakness that develops over weeks to months more in the proximal muscles, as evidenced by difficulty in walking up stairs, getting up from the chair or combing one’s hair³.

Mixed connective-tissue disease (MCTD) is a disorder with features of systemic sclerosis (SSc), lupus erythematosus, and dermatomyositis. U1ribonucleoprotein (RNP) antibodies are a specific marker of the disease(3). Patients with MCTD present with Raynaud’s phenomenon, represents the initial manifestation of the disease. During the course of the disease in some patients, the typical signs and symptoms of SLE develop and fulfill at least 4 of the American Rheumatism Association (ARA) criteria. In other patients, MCTD becomes systemic sclerosis that spreads to the face, scalp, and trunk, and the fingers become immobile, hard, and shiny. Sausage-shaped fingers, and swelling of the dorsa of the hands that never becomes sclerodactyly are the most typical features⁶.

In the present study , total of 40 cases of CTDs who fulfil the criteria were included. The demographic and clinical profile of our patients were comparable to other studies^{7,8}. Most of the CTDs show female preponderance in our study, with 33 (82.5%) female patients and remaining were males. Majority 17 patients (42.5%) were between 30-40 years age group⁹. Youngest one was 5 years boy and eldest was 62years. Incidentally both were cases of dermatomyositis . The disease frequency in our study was out of 40 , 25 (62.5%) were LE , 10 (25%) were Systemic sclerosis , 3 (7.5%) were patients of dermatomyositis and 2 (5%) were MCTD .

In LE patients, more than 80% of patients display skin symptoms sometimes during the course of disease¹⁰. Similarly all 25 (100%) patients of LE presented with cutaneous manifestations in our study.Malar rash was present in 11 patients (44%) , papulosquamous rash was present in 6 patients(24%) and 8(32%) patients show discoid rash and 1 case (4%)of LE profundus who presented with atrophy of cheeks. In other studies,malar rash was 29% in Rabbani et al¹¹, 60% in Edward et al¹², 56% in Mok et al¹³,58.9% in Ward et al¹⁴ and it was 35% in Kohli P et al¹⁵.

Papulosquamous rash was seen in 6(24%) cases while it was 39% in Parodi A et al study¹⁶and it was low (3%) in Parveen N et al study¹⁷.

Discoid rash in our study was present in 32% of patients and varied with other studies like Rabbani et al 14%, Mok et al 12% , Edward et al 10%, Parveen N et al 10%, Ward et al 7% and it was similar to Kohli P et al study which was 30%.

Photosensitivity in our study was found in 48% of patients , it was 48% in Ward et al, 42% in Kohli P et al, 35% in Mok et al , 31% in Edward et al and 6% in Rabbani et al.

Oral ulcers were seen in 8 patients (32%) in our study and it was 20% in Rabbani et al and Edward et al studies and 18% in Kohli P et al study (Table 5).

Table No.5: Correlation of cutaneous features of LE with various studies

Sl.No	Clinical features	Present study	Rabbani et al	Edward et al	Mok et al	Ward et al	Kohli P et al	Parveen N et al
1	Malar rash	44%	29%	60%	56%	58.9%	35%	-
2	Papulosquamous rash	24%	-	-	-	-	-	3%
3	Discoid rash	32%	14%	10%	12%	7%	30%	10%
4	Photosensitivity	48%	6%	31%	35%	48%	42%	-
5	Oral ulcers	32%	20%	20%	-	-	18%	-

In our study, Raynauds phenomenon was seen in 7 patients (28%), it was 39.6% in Cardinali C et al¹⁸, 32% in Malaviya AN et al¹⁹ and 12% in Parveen et al study. Non scarring alopecia was seen in 5 (20%) cases. 1 male and 1 female patient (8%) were presented with vasculitis, whereas it was 33.34% in Kole AK et al study⁹.

Among LE cases, 2 (8%) cases were Acute LE, 6 (24%) were sub acute cutaneous LE and 9 (36%) were CCLE and 8 (32%) were SLE.

The typical patient of Acute cutaneous LE presented with lesions above the neck or generalised. Malar rash or erythema or an edema over face with sparing of nasolabial folds seen after sun exposure²⁰. 2 (8%) cases of acute LE fulfill the above criteria, were females 11 years and 32 years old presented with fever, arthralgia, facial erythema and edema and purpuric rash and oral ulcers on palate. Both were ANA and ds DNA positive. Elder lady presented with albuminuria and purpuric rash over leg and biopsy proven vasculitis.

According to Gilliam and sontheimer, subset of Sub acute cutaneous LE was considered when lesions located over sun exposed areas were appeared as papulosquamous, annular, polycyclic plaques and were non scarring heal with pigmentary changes and majority associated with anti Ro/SS A, ANA and anti La/SS B antibodies^{20,21,23,24}. In present study 6(24%) cases were SCLE, of which 4 (16%) were females and 2 (8%) were males, presented with papulosquamous rash over sun exposed areas, photosensitivity, arthralgia and oral ulcers on palate were ANA +ve, among which 2 (33%) were Anti Ro/SSA +ve. Parodi A et al reported it was 71%¹⁶.

Chronic cutaneous LE includes Discoid LE, LE profundus and Chilblain lupus, in which DLE was common. It may be either localized or disseminated. Presented as well demarcated, erythematous, keratotic plaques with follicular hyperkeratosis at the center of lesion which heal with atrophy and scarring and pigmentation. Involves face and scalp in localized form, and upper trunk and extensors in disseminated form³. Mucosal involvement is around 25%²³. The risk of DLE going to SLE is 1.2% in localized form and 22% in disseminated form. LE profundus present as firm nodules present beneath normal skin and followed by atrophy of the fat over that area³. In present study, 9 (36%) cases were CCLE. Out of which 2 were male and 7 were females. One male patient presented with disseminated DLE and one female patient with LE profundus with atrophy of cheeks. Rest of the 5 female patients and 1 male patient presented with discoid lesions over face and scalp. Among 9(36%) cases, 3(12%) patients fulfil the SLICC 2012 criteria for SLE who presented with photosensitivity, oral ulcers, abnormalities in complete blood picture, proteinuria, ANA +ve and Anti ds DNA +ve. This is lower when compared to Insawang M study(45.4%)²⁴.

Systemic lupus erythematosus is a multisystem disease, when patients met 4 out of 11 of SLICC 2012 criteria³. More than 80% were ANA+ve. Renal involvement is associated with Anti ds DNA commonly. Anti Sm antibodies are associated with neurological, pulmonary, renal involvement and correlate poor prognosis²⁵.

Among 25 cases of LE, 8 (32%) cases presented with systemic involvement. Neurological involvement was present in 3(12%) cases, 2 were males and both are suffering from psychosis presented with photosensitivity, arthralgia and fever. One male patient who presented with chronic punched out leg ulcers, ds DNA +ve, Anti Sm +ve and biopsy showed vasculitis, those ulcers were healed in 3 months with PRF treatment. One female patient presented with malar rash, photosensitivity, fever, arthralgia, developed seizures (GTCS) 2 months after cutaneous manifestations (ANA +ve, Anti Sm 3+, n RNP 2+, ds DNA -ve). Renal involvement was present in 5 patients(20%) indicating it was common systemic involvement in our study. Out of 5 cases, all were females, 1 was biopsy proven DPGN (ANA +Ve, ds DNA +ve, Anti Sm +ve). It was similar to Kadiru RA et al study⁸. Remaining cases were presented with hypoalbuminemia, proteinuria, hypertension (Anti Sm +ve, Anti ds DNA +ve) and were denied for renal biopsy.

In our study of 40 cases of CTDs, Systemic sclerosis were 10(25%) and 8(80%) were limited SSc, out of which 7 were females and one was male. 2 cases of Diffuse SSc were females with 20 years and 32 years respectively having respiratory involvement and HRCT proven ILD (Scl 70 3 +ve and Scl 70 1+ve respectively). ILD seen in 66.7% of diffuse SSc in Arrakal G et al study²⁶. Out of 8 limited SSc, one male patient having GIT involvement showing dilated esophagus who is symptomatic (ANA +, Anti centromere + and Anti Ro+ve). In one female patient with limited SSc, cardiac involvement was there showing pericardial effusion in 2D ECHO(Anti centromere +ve). Pericardial effusion seen in 3.6% in Arrakal G et al study²⁶.

In present study, all 10 (100%) patients of systemic sclerosis were presented with cutaneous manifestations. Sclerosis was present in all 10(100%) cases, salt and pepper pigmentation in 9(90%) cases,

Raynauds phenomenon in 8 (80%) cases, Digital tip ulcers in 5(50%) cases, Radial furrowing in 4 (40%) cases, Digital pits ,parrot beak nose with decreased forehead wrinkling in 3 (30%) cases and bulbous fingers in 2 (20%) cases. These features are compared with other studies ^{27,28,29}.(Table 6)

Table No. 6: Correlation of cutaneous features of Systemic sclerosis with various studies

Sl.No	Clinical features	Present study	Ghosh Sk et al ²⁷	Kodali S et al ²⁸	Sharma VK et al ²⁹
1	Sclerosis	100%	82.6%	100%	100%
2	Skin dyspigmentation	90%	86.9%	50%	91%
3	Raynaud phenomenon	80%	84.8%	83.3%	92.9%
4	Finger tip ulcers /scars	80%	63%	-	58.6%

Among 3 cases of dermatomyositis , 2 were males and 1 was female. One case of Juvenile dermatomyositis , who was 5 years old boy presented with fever on and off, weakness of extremities, and painful skin ulcers over trunk for 1.5months with periorbital edema. ANA positive and biopsy proven Inflammatory myopathy was present. All CKMB , Serum Creatinine kinase levels were raised. Another male patient aged 62 years presented with weakness of lower limbs and rash. Biopsy proven inflammatory myopathy was present. One female patient aged 18 years , presented with fever, heliotrope rash, and non healing ulcers over elbow (vasculitis).

Among 2 MCTD patients , both were females presented with Raynauds phenomenon, edema of hands ,arthralgias ,rash ,oral ulcerations (ANA +ve, ds DNA +ve, Anti Sm +ve and U1 RNP 1:1600) . Cardiac , respiratory and renal parameters were normal in both patients.

V. Conclusion

- Our study reviewed various cutaneous manifestations of CTDs .
- Most of the CTDs in our study occurred between 31-40years.
- Female patients outnumbered males.
- LE was the commonest CTD.
- Acute LE was correlated more often with systemic involvement.
- Renal system being the most common systemic involvement among LE.
- The incidence of systemic involvement in CCLE is around 12%.
- Sclerosis and dyspigmentation were most common manifestations of Systemic sclerosis.

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Malar Rash



Malar Rash



Malar Rash



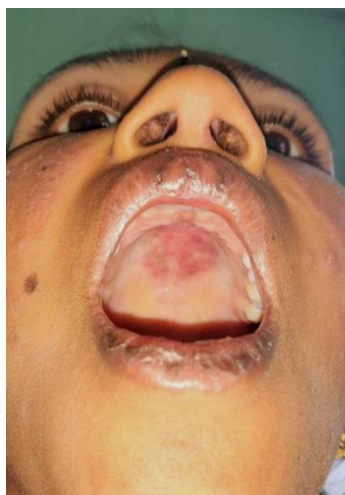
Malar Rash



Discoid rash over face



Discoid rash over right ear



Oral ulcers over palate



Oral ulcers (palate)



Papulosquamous rash on chest in SCLE



Papulosquamous rash over extremities



SLE presented with punched out ulcers (Vasculitis)



Healing ulcer - After PRF



Acute LE with purpuric lesions on lower limbs



Scarring Alopecia



Sclerosis of skin



Skin dyspigmentation with typical face showing radial furrow



Digital tip scars



Digital tip ulcers



Periorbital erythema



Vasculitic ulcers over right elbow in Dermatomyositis



Puffy fingers in MCTD

References

- [1]. Jan p.Dutz,Heidi T.jacobe.Rheumatologic Dermatology.In: Bologna JL,SchafferJV,editors.Bologna Text Book of Dermatology,China:Elsevier; 2018,p.648-92.
- [2]. Kuhn A, Sticherling M, Bonsmann G. Clinical manifestations of cutaneous lupus erythematosus. *JDDG: Journal der Deutschen B Dermatologischen Gesellschaft.* 2007 Dec;5(12):1124-37.
- [3]. Mark Goodfield. Lupus erythematosus. In: Griffiths CE BJ, Bleiker T,Chalmers R,Creamer D, editor. *Rooks Textbook of Dermatology.* 9th ed. Oxford: Wiley Blackwell; 2016. p. 51-54.
- [4]. Krieg T, Takehara K. Skin disease : a cardinal feature of systemic sclerosis. *Rheumatology* 2009;48:iii14-18.
- [5]. Holden DJ, Brownell AKW, Fritzler MJ. Clinical and serological features of patient with polymyositis or dermatomyosistis. *Can med assoc J* 1985;132:649-53.
- [6]. Gunnarsson R, Molberg O, Gilboe IM, Gran JT. The prevalence and incidence of mixed connective tissue disease: a national multicentre survey of Norwegian patients. *Ann Rheum Dis.* 2011 Jun, 70(6):1047-51.
- [7]. Jethwa M, Mehtha H. A study of mucocutaneous manifestations in autoimmune connective tissue disorders at tertiary care centre. *J Evid Based Med Healthc* 2017;4:2701-5.
- [8]. Kaduru RA, Hegde SP, Shenoy MM. An observational cross-sectional study of varied clinical manifestations of connective tissue disorders and their association with antinuclear antibodies in a tertiary care center. *Indian Dermatol Online J* 2019;10:413-7.
- [9]. Kole AK, Ghosh A. Cutaneous manifestations of systemic lupus erythematosus in a tertiary referral center. *Indian journal of dermatology.* 2009 Apr;54(2):132.
- [10]. Grönhagen CM, Nyberg F. Cutaneous lupus erythematosus: An update. *Indian dermatology online journal.* 2014 Jan;5(1):7.
- [11]. Rabbani MA, Siddiqui BK, Tahir MH, Ahmad B, Shamim A, Shah SM, Ahmad A. Systemic lupus erythematosus in Pakistan. *Lupus.* 2004 Oct;13(10):820-5.
- [12]. Edwards CJ. Lupus in Singapore. *Lupus.* 2001 Dec;10(12):889-91.
- [13]. Mok CC, Lau CS. Lupus in Hong Kong Chinese. *Lupus.* 2003 Sep;12(9):717-22.
- [14]. Ward MM, Studenski S. Clinical manifestations of systemic lupus erythematosus: identification of racial and socioeconomic influences. *Archives of internal medicine.* 1990 Apr 1;150(4):849-53.
- [15]. Kohli P, Sharma K, Tolani A. A study of cutaneous manifestations of systemic lupus erythematosus in Malwa region of India. *International Journal of Research.* 2018 Apr;4(2):230.
- [16]. Parodi A, Caproni M, Cardinali C, Bernacchi E, Fuligni A, De Panfilis G, Zane C, Papini M, Veller FC, Vaccaro M, Fabbri P. Clinical, histological and immunopathological features of 58 patients with subacute cutaneous lupus erythematosus. *Dermatology.* 2000;200(1):6-10.
- [17]. Parveen N, Das DK, Haque FM, Haque MN. Cutaneous manifestations of systemic lupus erythematosus. *Journal of Medicine.* 2007;8(2):44-8.
- [18]. Cardinali C, Caproni M, Bernacchi E, Amato L, Fabbri P. The spectrum of cutaneous manifestations in lupus erythematosus-the Italian experience. *Lupus* 2000;9:417-23
- [19]. Malaviya AN, Singh RR, Kumar A, De A, Aradhya S. Systemic lupus erythematosus in northern India: a review of 329 cases. *The Journal of the Association of Physicians of India.* 1988 Aug;36(8):476-80.
- [20]. Gilliam JN, Sontheimer RD. Distinctive cutaneous subsets in the spectrum of lupus erythematosus. *J Am Acad Dermatol* 1981;4:471-5.
- [21]. Lin JH, Dutz JP, Sontheimer RD, Werth VP. Pathophysiology of cutaneous lupus erythematosus. *Clin Rev Allergy Immunol* 2007;33:85-106
- [22]. Provost TT, Watson R. Anti-Ro (SS-A) HLA-DR3-positive women: the interrelationship between some ANA negative, SS, SCLE, and NLE mothers and SS/LE overlap female patients. *J Invest Dermatol* 1993;100:14-20S
- [23]. In: Kuhn A, Lehmann P, Ruzicka T, editors. *Cutaneous Lupus Erythematosus.* Dusseldorf: Springer; 2005.
- [24]. Insawang M, Kulthanan K, Chularojanamontri L, Tuchinda P, Pinkaew S. Discoid lupus erythematosus: description of 130 cases and review of their natural history and clinical course. *Journal of Clinical Immunology and Immunopathology Research.* 2010 Apr 30;2(1):1-8.
- [25]. Antolin J, Amerigo MJ, Cantabrana A, Roces A, Jimenez P. Systemic Lupus Erythematosus: clinical manifestations and immunological parameters in 194 patients: sub-group classification of SLE. *Clin Rheumatol* 1995;14:678-85
- [26]. Arakkal G, Chintagunta SR, Chandika V, Damarla SV, Manchala S, Kumar BU. Cardio-pulmonary involvement in systemic sclerosis: A study at a tertiary care center. *Indian Journal of Dermatology, Venereology, and Leprology.* 2017 Nov 1;83(6):677.
- [27]. Ghosh SK, Bandyopadhyay D, Saha I, Barua JK. Mucocutaneous and demographic features of systemic sclerosis: A profile of 46 patients from Eastern India. *Indian journal of dermatology.* 2012 May;57(3):201.
- [28]. Kodali S, Reddy LV, Lavanya M, Sravanthi K, Chary NN. A clinical study of connective tissue diseases. *Lupus.* 2015;1(12.50):7.
- [29]. Sharma VK, Trilokraj T, Khaitan BK, Krishna SM. Profile of systemic sclerosis in a tertiary care center in North India. *Indian Journal of Dermatology, Venereology, and Leprology.* 2006 Nov 1;72(6):416.