Clinical Profile Of Cutaneous Manifestations In Various Autoimmune Connective Tissue Diseases

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Abstract: Background: Autoimmune Connective Tissue Diseases (AICTDs) are a heterogeneous group of autoimmune disorders having overlapping clinical features. Skin is often involved and it may be the earliest sign of the systemic disease. Aims: This study highlights the various cutaneous manifestations of common AICTDs. Material and Methods: A hospital-based cross-sectional study was carried out for a period of two years on 120 patients of AICTDs in dermatology OPD/ward at tertiary care hospital. Detailed history taking, examination and relevant laboratory tests were performed. Results: Majority of the patients had lupus erythematosus (LE) (41.67%) followed by, mixed connective tissue disease (MCTD) (28.33%), systemic sclerosis (SSc) (12.5%) and morphea (10.83%). Overall, the most common presentation was photosensitivity (39.16%) followed by raynaud's phenomenon (33.33%), oral lesions (29.16%), hide bound skin (29.16%), discoid rash (29.16%) and malar rash (25.83%). Among LE patients, systemic lupus erythematosus (SLE) (18.33%) was the commonest variant and malar rash (77.27%) and photosensitivity (77.27%) were the commonest presentations. Hide bound skin, microstomia and sclerodactyly were seen in most patients of systemic sclerosis (SSc). Antinuclear antibodies were positive in 100% excluding morphea, DLE and DDLE patients. Anti-dsDNA and anti-Sm antibodies were positive in 68.18% and 40.9% of SLE patients, anti-Scl 70 antibody was positive in 53.33% of SSc patients. Conclusion: A deep thorough understanding of cutaneous manifestations of AICTDs is necessary for early diagnosis and efficient management, hence better prognosis. [Bhindora P Natl J Integr Res Med, 2023; 14(2): 08-15, Published on Dated: 15/03/2023]

Key Words: Connective Tissue Diseases, Lupus Erythematosus, Systemic Sclerosis, Photosensitivity, Raynaud's Phenomenon

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Introduction: The autoimmune connective tissue diseases (AICTDs) are a group of polygenic disorders due to autoimmune process and sometimes with overlapping clinical features[1].

The essential feature of autoimmune disease is tissue injury caused by immunologic reaction against own tissue. Autoimmunity is present in all individuals but autoimmune diseases occur only in whom breakdown of one or more basic mechanisms regulating immune tolerance result in self reactivity[2].

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 AICTDs and certain signs often represent the early stage of disease by its presenting symptoms. Therefore, knowledge of cutaneous manifestations is essential for accurate early diagnosis and to alert the clinicians for early intervention and effective management so that debilitating systemic complications can be prevented.

Various AICTDs showing cutaneous manifestations include lupus erythematosus (LE), systemic sclerosis (SSc), dermatomyositis, Sjogren's syndrome, mixed connective tissue disease (MCTD), overlap syndrome and undifferentiated connective tissue disease (UCTD).

Material & Methods: The present study is prospective, open and observational study carried out on 120 patients of AICTDs in the department of dermatology, venereology and leprosy at P.D.U Govt. Medical College and Hospital, Rajkot for 2 years from October 2019 to september2021.

Inclusion Criteria: Patients of all ages and both

sex with AICTDs having cutaneous manifestations presented to dermatology opd, admitted in ward and referred from other wards were included.

Exclusion Criteria: Patients who had not given consent for participation.

Methodology: After informed consent detailed history regarding onset, duration and progress of mucocutaneous lesions, examination, clinical photographs and relevant laboratory investigations including ANA and ENA profile were done.

Cases of Systemic Lupus erythematosus were diagnosed according to Systemic Lupus International Collaborating Clinics (SLICC) criteria.

Systemic sclerosis patients were diagnosed according to Modified Rodnan score, a total of 17 sites were graded from '0' for no tethering up to '3' for severe along with specific autoantibodies.

MCTD patients were diagnosed according to Alarcon Segovia criteria along with diagnostic criteria for mixed connective tissue disease 2019, from the Japan research committee of the ministry of health, labour, and welfare for systemic autoimmune diseases.

Overlap syndrome was considered in patients when they clinically manifested with features of any two CTDs supported by serological positivity and absence of U1RNP antibodies. UCTD was considered in patients not fulfilling criteria for a specific AICTD and who fulfilled the following criteria (a) signs and symptoms suggestive of a connective tissue disease (CTD), but not fulfilling criteria for a defined AICTD (b) Positive ANA on two separate measurements controls and (c) a disease duration of at least 3 years[3].

Ethical approval was taken from institutional ethics committee.

Results: In the present study of 120 cases of AICTDs there were 50(41.67%) cases of LE (22 SLE, 3 SCLE, 10 DLE and 15 DDLE), 34(28.33%) of mixed connective tissue disease, 28(23.34%) of scleroderma, 2(1.66%) of undifferentiated connective tissue disease and 2(1.66%) of dermatomyositis. Overall M: F ratio was 1:3.44 (male 27, female 93) with female predominance (Table 1). All the cases of MCTD, UCTD, overlap syndrome, secondary Sjogren were females. Maximum cases 35(29.16%) were found in the age group of 21-30 years followed by 29 (24.16%) cases in the age group of 41-50 years with least incidence below 10 years (1.25%) (Figure 1).

Table 1: Overall Types And Sex Wise Distribution Of AICTDs

AICTDs		Sex Wise No. Of Patients (%)		Total No. Of Patients (%)
		M	F	
LE		16(32%)	34(68%)	50(41.67%)
	SLE	0(0%)	22(100%)	22(18.33%)
	SCLE	2(66.66%)	1(33.33%)	3(2.5%)
	DLE	8(80%)	2(20%)	10(8.33%)
	DDLE	6(40%)	9(60%)	15(12.5%)
Scleroderma		9(32.14%)	19(67.86%)	28(23.34%)
	Systemic Sclerosis	4(26.66%)	11(73.33%)	15(12.5%)
	Morphea	5(38.46%)	8(61.54%)	13(10.83%)
Dermatomyositis		1(50%)	1(50%)	2(1.66%)
MCTD		0(0%)	34(100%)	34(28.33%)
UCTD		0(0%)	2(100%)	2(1.66%)
Overlap Syndrome		1(50%)	1(50%)	2(1.87%)
Secondary Sjogren's syndrome		0(0%)	1(100%)	1(0.83%)
Cutaneous manifestations in RA		0(0%)	1(100%)	1(0.83%)
Total		27(22.5%)	93(77.5%)	120(100%)

Figure 1: Age Wise Distribution Of AICTDs

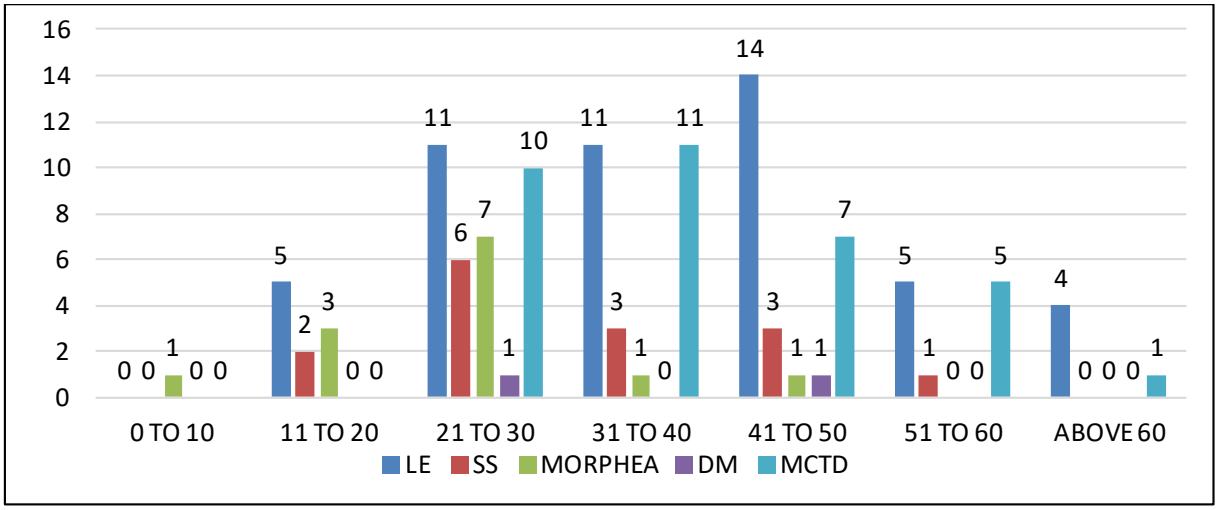


Table 2: Cutaneous Features Of SLE, MCTD And SSC With Comparison To Other Studies

	SLE			MCTD		Systemic Sclerosis	
Cutaneous Features	Present Study (N=22) %	Kohli P et al[8] 2018 (N=100) %	Maheshwari et al[6] 2017 (N=110) %	Present Study (N=34)%	Sen et al[14] 2014 (N=23) %	Present Study (N=15) %	Sharma et al[13] (N=100) %
Malar Rash	77.27	35	66.36	26.47	21.7	-	-
Discoid Lesions	22.72	30	20	14.70	8.7	-	-
Photosensitivity	77.27	42	60	29.41	-	-	-
Oral Lesions	68.18	58	70	32.35	8.7	-	-
Raynaud's Phenomenon	13.63	12	10	67.64	78	86.67	92.9
Non Cicatricial Alopecia	36.36	10	80	50	8.7	-	-
Cicatricial Alopecia	9.09	-	10	0	-	-	-
Lupus Hair	18.18	-	-	8.82	-	-	-
Bullous Lesions	4.5	2	-		-	-	-
TEN- Like Peeling	13.63	-	-		-	-	-
Vasculitis	4.5	-	-	14.70	-	-	-
Edema Face	22.72	-	-	50	-	-	-
Palmar Erythema	22.72	-	-	20.58	-	-	-
Nail Changes	18.18	-	16.36	26.47	4.3	46.67	-
Hide Bound Skin	-	-	-	55.88	-	100	98.5
Puffy Hands	-	-	-	70.58	39.1	-	-
Fingertip Ulcer	-	-	-	14.70	21.7	-	-
Gangrene	-	-	-	11.76	4.3	20	6.7
Pigmentary Changes	-	-	-	26.47	8.7	86.67	91
Reduced Mouth Opening	-	-	-	-	-	80	55.5
Pinching Of Nose	-	-	-	-	-	60	-
Purse String Mouth	-	-	-	-	-	53.33	-
Expressionless Face	-	-	-	-	-	80	-
Sclerodactyly	-	-	-	-	-	66.67	46.6
Stellate Ulcer	-	-	-	-	-	53.33	58.6
Stellate Scarring	-	-	-	-	-	80	-
Salt & Pepper Skin	-	-	-	-	-	60	51.2
Telangiectasia	-	-	-	-	-	20	36.8
Calcinosis Cutis	-	-	-	-	-	13.33	-

Table 4: ENA Profile In Various Aictds

	SLE (22)	SCLE (3)	SS (15)	MCTD (34)	UCTD (2)	Overlap (2)	Secondary Sjogren's (1)
Anti-DS DNA	15	3	0	3	0	0	0
Anti -SM	9	1	1	8	0	1	0
Anti -RNP	7	1	0	15	2	0	0
Anti -SSA	5	2	8	7	0	1	1
Anti -SSB	3	1	3	5	0	0	0
Anti -Ribosomal	7	2	0	4	0	0	0
Anti- Histone	3	0	0	4	0	0	0
Anti-Nucleosome	4	0	0	6	1	1	0
Anti M2	1	0	1	0	0	0	0
Anti U1 RNP	6	0	0	34	0	0	0
Anti CENP	0	0	2	2	0	0	0
Anti SCL-70	0	0	8	2	0	0	0
Anti JO	0	0	1	3	0	1	0
Anti PM-SCL	0	0	5	0	1	1	0

Figure 2: Malar Rash Sparing Nasolabial Folds In SLE

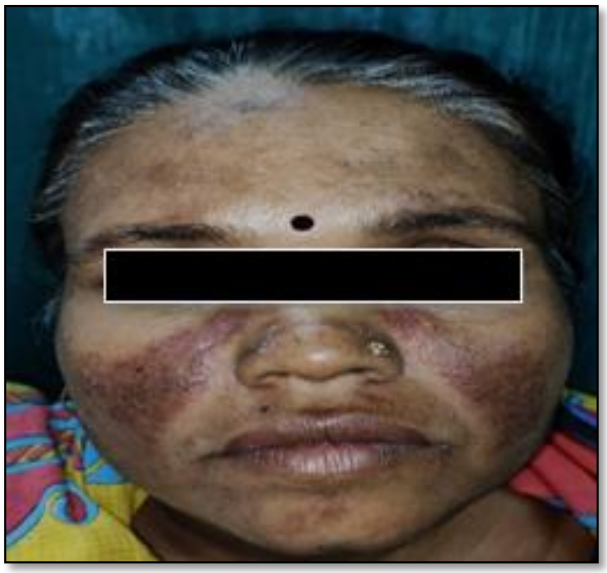


Figure 3: Oral Ulcers Over Hard Palate In SLE

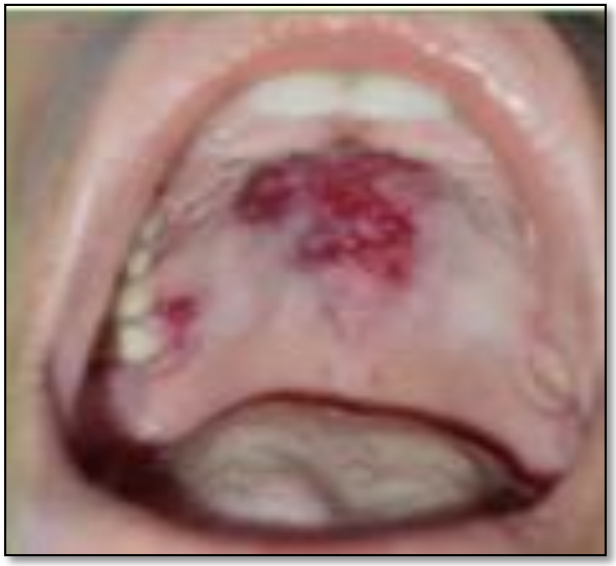


Figure 4: Vasculitic Lesions In SLE

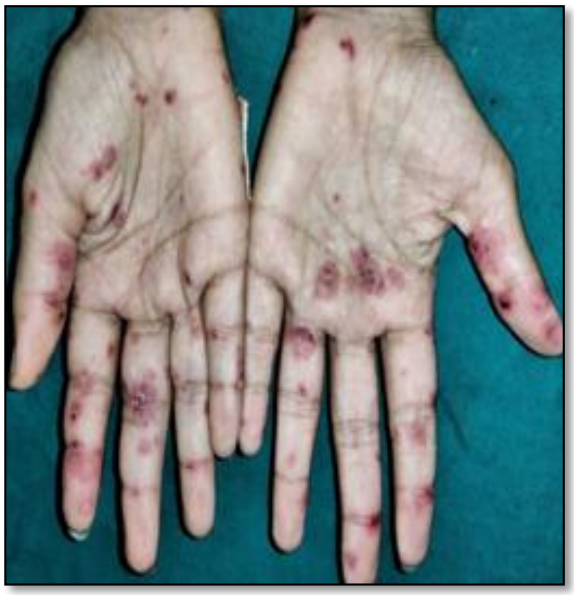


Figure 5: Salt Pepper Pigmentation In Ssc

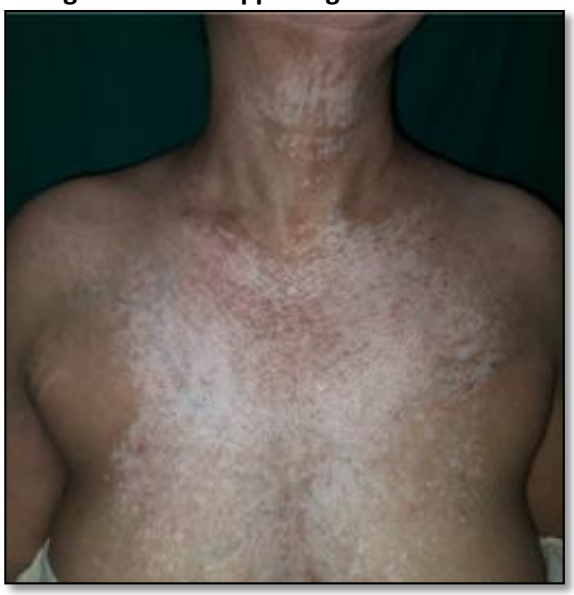


Figure 6: Raynaud's Phenomenon In MCTD

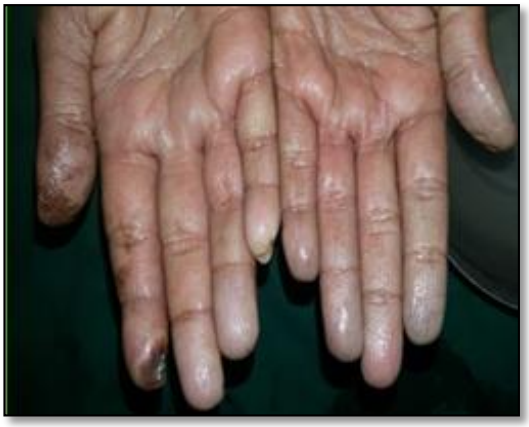
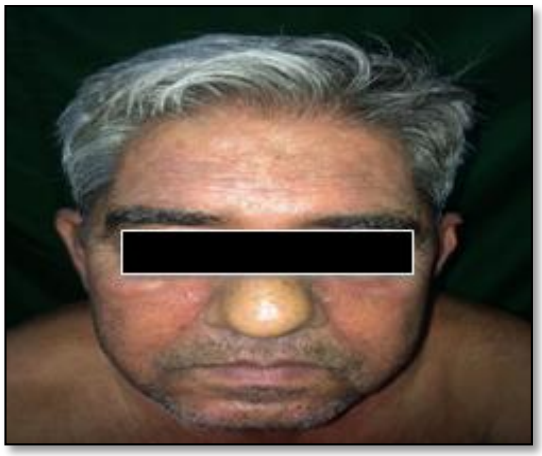


Figure 7: Heliotrope Rash Of Dermatomyositis



Overall, most common presentation was photosensitivity in39.16% followed by raynaud's phenomenon in 33.33%, oral ulceration, discoid rash, hide bound skin in 29.16% each, malar rash in 25.83% and non-cicatricial alopecia in 20.83%.

All the cases of SLE, SCLE, DLE, DDLE, MCTD and SSc were presented with cutaneous features as their chief complaint.

Out of 50 patients with LE, SLE was the commonest in 44%(N=22) cases followed by DDLE 30% (N=15), DLE 20%(N=10), SCLE 6%(N=3).

The M:F ratio of LE in general was 1:1.75 with all cases were females in SLE, while male preponderance was observed among DLE and DDLE cases. In SLE most common affected age group was 21-30 years in 40.9% cases while in cases of DLE and DDLE it was 41-50 years.

In SLE photosensitivity and malar rash were present in 77.27% of cases each. Discoid rash was present in 22.72% cases, it was mainly located over exposed areas such as face, upper chest and upper back (Figure 2). Oral ulceration was seen in 68.18%, of which 92.59% were palatal in location (Figure 3). Majority of the patients had hair fall, manifested as presence of non-cicatricial alopecia in 36.36% and cicatricial alopecia in 9.09% cases. Palmar erythema was seen in 5 (22.72%). Raynaud's phenomenon is a less common finding in SLE with 3(13.63%) cases exhibiting Raynaud's phenol menon.

One important observation in a female patient with SLE was generalized maculopapular rash with peeling of skin simulating Toxic Epidermal Necrolysis (TEN). Vasculitic lesions were seen in 4.5% cases (Figure 4).

Nonspecific nail findings, such as thinning of nail plate, onychomycosis, periungual haemorrhage was seen in 6(18.18%) cases. Out of 3 patients of SCLE, photosensitivity and annular polycyclic lesions were present in 100 % cases, oral ulceration in 66.66% cases.

Discoid skin lesions over face, neck, scalp, back, chest and extremities were the cardinal features of DLE & DDLE, seen in 100% cases. Other cutaneous features of DLE and DDLE were photosensitivity, malar rash, oral ulceration and cicatricial alopecia.

Out of 28 cases of scleroderma, 15(53.57%) cases of SSc, 13(46.42%) cases of morphea were there with M: F ratio was 1:4.25. Almost all the cases of SSc had cutaneous features at presentation with raynaud's phenomenon and skin involvement was almost universal in SSc. Hidebound skin was seen in all 15(100%) cases.

Next common manifestation were pigmentary changes in 13 (86.67%) cases, of which salt and pepper appearance was seen in 69.23% patients followed by diffuse hyperpigmentation in 4(30.76%) cases (Figure 5).

Reduced mouth opening and expressionless face were present in 12(80%) cases each. Majority of the patients had stellate scar (80%). Fingertip ulcers were less commonly observed in 8(53.33%). Contracture of the fingers leading to hands/feet deformities were observed in 11(73.33%) cases.

Nail changes were seen in 46.67% cases, most of them had beaking of nail plate. Diffuse non cicatricial alopecia was seen in 15% of cases. Out of 13 cases of morphea 6(46.15%) were of plaque type, 2(15.38%) cases of generalized and linear variant each while, encoup de sabre, hemifacial

atrophy, atrophoderma of pasini-pierini was seen in 1(7.69%) case each.

Among 34 cases of MCTD majority 20(58.82%) cases were in 31-40 years of age group with all were females. All cases had cutaneous finding at presentation, the most common among them was puffy hands in 24(70.58%) patients.

Raynaud's phenomenon was present in 23(67.64%) (Figure 6). Joint pain without swelling was present in (44.11%) and 17.64% had joint pain with swelling. Muscle weakness was present in 32.35% cases. Cutaneous vasculitis was present in 5(14.70%) cases with 1 having vasculitic ulcers.

There were 2 cases of adult onset dermatomyositis with M: F ratio1:1. Both (100%) cases presented with proximal muscle weakness and heliotrope rash with periorbital edema (Figure 7).

Gottron's papules were present in both the cases. Holster's sign and shawl sign were present in 1 case each. V sign was present in 1 case and nail changes were present in both cases.

Out of 2 patients of overlap syndrome one patient presented at 40years and another at 60 years. One was male and one was female. Cutaneous features common to all of them was lid edema. Case of SLE+ Sjogren syndrome showed photosensitivity, malar rash, salt and pepper pigmentation, puffy fingers and facial edema. All cases of UCTD were females ranging from 40 years to 50 years with average age at presentation was 42 years. 1 case presented with photosensitivity, 1 with hidebound skin and 1 with Raynaud's phenomenon, but none of them fit into the criteria for particular AICTD.

There was 1 case of secondary sjogren's syndrome who was female with 28 years of age. It was associated with SLE and TEN like peeling. Patient had history of severe dryness of eyes and gritty sensation which was confirmed with Schirmer's test. She had dry mouth and difficulty initiating swallowing.

ANA positivity was seen in all the cases. In SLE most common ANA pattern was homogenous 20(90.09%) followed by speckled pattern in 2(9.09%). In SCLE all 3 had homogenous pattern. Among 15 cases of SSc most common pattern was speckled in 10(66.66%) cases. In MCTD speckled pattern was most common in 27(79.41%) cases, followed by homogenous in 5(14.70%) cases. ENA profile was done and multiple antibodies were present in single patient.

In SLE anti-dsDNA antibody was present in 15(68.18%), anti-SM in 9(40.90%), anti RNP and anti-ribosomal antibody were in 7(31.81%) and anti-nucleosome in 4(18.18%) cases. In systemic sclerosis, anti-SCL70 was present in 8(53.33%) cases, anti PM-SCL was present in 5(33.33%).

Among 2 cases of overlap syndrome, anti SM plus anti-SSA was seen in one case.

Discussion: Cutaneous Lupus Erythematosus, Scleroderma, Dermatomyositis, MCTD and UCTD are AICTDs which exhibit cutaneous with systemic manifestations and varied presentation and each entity makes classification of AICTDs difficult and challenging to the clinician especially in case of Overlap & Undifferentiated connective tissue disorders. Detailed types and sex wise distribution of different AICTDs are enumerated in table 1.

Out of 120 cases, LE was most common AICTD with 50(41.67%) cases followed by MCTD in 34(28.33%), scleroderma in 28(23.34%), which is comparable with Subba DM et al and Begum NT et al in which LE was most common but second most common entity was SSc followed by MCTD.

Maximum cases 35(29.16%) were found in age group of 21-30 years, while Begum NT et al reported maximum cases between 31-40 years.

Youngest patient was 9 years old and oldest was 80 years old female. Majority 93(78.33%) were females which is comparable with Subba DM et al and Begum NT et al studies[4,5].

In patients of LE female to male ratio was 2.12:1, while in SLE all were females (F:M 1:0) compared to Maheshwari et al with 9:1 and Kosaraju et al with 13:1 ratio6,7. Average age of presentation in SLE was 28 years comparable with other study.

All cases of SLE, SCLE, DLE and DDLE presented with cutaneous features as their chief complaint. In SLE, photosensitivity and malar rash were present in 77.27% of cases each, which was

higher than Maheshwari et al (66.36%) Kohli P et al study (35%)[8]. Discoid rash was present in 22.72% cases which was mainly located over exposed areas, such as face, upper chest, upper back, lower legs. The findings were comparable to both Maheshwari et al (20%) and Kohli P et al (30%)[6,8]. Majority of the patients had hair fall, manifested as non-cicatricial alopecia in 36.36%which was higher than Kohli P et al(10%) while it was higher in case of Maheshwari et al (80%) and lupus hair in 18.18%.Oral ulceration was observed in 68.18%, which was comparable with Maheshwari et al(70%) and most of them were palatal in location[Table 2].

Raynaud's phenomenon is a less common finding in SLE. In our study we had 3(13.63%) cases exhibiting Raynaud's phenomenon, which was comparable to Kohli P et al (12%), Maheshwari et al (10%). Malaviya et al from north india noted Raynaud's Phenomenon in 32% and Heimovski et al reported 49.1%[9,10].

This variation can be attributed to climatic condition of that particular region. Sinha et al reported cutaneous manifestation of SLE in 85 % of patients with photo-sensitivity in 75 %, discoid rash in 41.66%, raynauds and malar rash in 27.77% cases each while Nithya Gayathri Devi et al reported cutaneous manifestation in 45% with photo-sensitivity in 98% cases[11,12].

Among the cases of SSc raynaud's phenomenon and skin involvement is almost universal. Hidebound skin was seen in all 15(100%) cases.

This was comparable to the observation by Sinha et al (100%). The aggravation of Raynaud's phenomenon is higher during winter probably because of the cold induced vasoconstriction.

Pigmentary changes (86.67%) was the next most common changes of which salt and pepper appearance was mostly seen in 9(69.23%) patients which was similar with Begum NT et al and more than Sinha et al.

Reduced mouth opening and expressionless face with equal incidence of 80%. Majority of the patients had stellate scar (80%).

Though fingertip ulcers were less commonly observed in (53.33%) our study, its incidence was 100% in Sinha et al study. Contracture of the fingers leading to hands/feet deformities were observed in 73.33% cases which was consistent with the finding of Sharma et al (64.6%)[13].

Gangrenous changes were more common in our study (20%) as compared to Sharma et al (6.7%) which may be due to vibratory machinery work and smoking. Telangiectasia was present in 20% which was comparable with Sharma et al and nail changes were seen in 46.67% cases, most of them had beaking of nail plate. Diffuse non-cicatritial alopecia was seen in 15% of cases.

In MCTD, all the cases had cutaneous findings at presentation, the most common was puffy hands 24(70.58%) followed by oral ulceration in 11(32.35%), photosensitivity in 10(29.41%), malar rash in 9(26.47%) which is comparable to Sinha et al study.

Raynaud's phenomenon was present in 23(67.44%) cases, palmar erythema in 7(20.58%), pigmentary changes in 9(26.47%) cases. Hide bound skin was observed in 19(55.88%) patients and non-cicatricial alopecia in 17(50%) patients.

In Sen et al they observed raynaud's phenomenon in 78%, puffy hands in 39.1%, malar rash in 21.7 %, finger-tip ulcer in 21.7%14.

ANA positivity was seen in all cases which is correlating with Subba DM et al study. In SLE anti-sm antibodies were positive only in 9 (40.90%) while Subba DM et al study reported 55.5%. Anti-sm antibody reported to be associated with Raynaud's phenomenon and malar rash[15].

Presence of anti-dsDNA antibodies was the hallmark of SLE was seen in 15(68.18%) while in Subba DM et al study it was 35.5%.

Anti-dsDNA antibody was strongly associated with renal involvement in patients with lupus. Anti-Scl 70 antibodies were positive in 8(55.33%) of patients while Purnima G et al reported 68% and 35%[16].

All the patients of MCTD were positive for anti U1RNP which was same with Subba D M et al [Table 3 & 4].

Limitation Of Study: Small size of samples due to few patients directed towards rheumatology department directly, ENA profile of every patients could not be done.

Conclusion: Our study reviewed various cutaneous manifestations of AICTDs. They can present with various specific and non-specific cutaneous lesions and can be earliest sign of the disease.

Maximum number of patients (29.16%) belonged to 21-30 years. Females (77.5%) outnumbered males in our study (22.5%). LE was commonest AICTDs with 41.67% cases.

Dermatologists are at a strategic position in the diagnosis and treatment of AICTDs, so comprehensive knowledge of cutaneous as well as systemic manifestations of various AICTDs will be helpful for the early diagnosis and efficient management of the patients to minimize systemic complications and to prevent morbidities in AICTD patients.

Henceforth, the overall management should be carried out using a multi-disciplinary approach.

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Conflict of interest: None
Funding: None
Cite this Article as: Bhindora P, Patel Y, Patel B, Bhuptani N. Clinical Profile Of Cutaneous Manifestations In Various Autoimmune Connective Tissue Diseases. Natl J Integr Res Med 2023; Vol.14(2): 08-15