The intersection of dermatology and immunology: Cutaneous manifestations, autoantibodies and quality of life in connective tissue diseases

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ABSTRACT

Introduction: Connective tissue diseases (CTDs) are autoimmune diseases with multiorgan involvement. CTDs present with a heterogeneous clinical manifestation, especially in the cutaneous system. This study aimed to describe the common cutaneous manifestations of CTDs, to determine the association with antinuclear antibody (ANA) and other associated antibodies, and to assess the impact of CTDs on patient's quality of life (QOL).

Material and Methods: This was a cross-sectional study conducted among patients 18 years and above, with a confirmed diagnosis of systemic lupus erythematosus (SLE), systemic sclerosis, dermatomyositis, mixed connective tissue disease (MCTD) or overlap syndrome, who attended the rheumatology clinic at Hospital Sultan Ismail Johor Bahru between March 2023 to June 2023. The assessment instrument used was the Dermatology Quality Life Index (DLQI).

Results: Among 79 patients recruited, the majority were females with a mean age of 39 ± 14.5 years. Malay was the predominant ethnic group. SLE was the most common CTD (64 patients, 81%), followed by systemic sclerosis (six patients, 7.6%), overlap syndrome (four patients, 5.1%), dermatomyositis (four patients, 5.1%) and MCTD (one patient, 1.3%). All patients had cutaneous involvement with photodermatitis being the commonest cutaneous manifestation (65 patients, 82.3%). ANA and anti-double stranded DNA (dsDNA) positivity were significantly associated with SLE while anti-scl70 and anti-centromere antibodies (ACA) were strongly associated with systemic sclerosis ($p < 0.05$). The presence of anti-dsDNA and anti-scl70 were significantly associated with renal involvement and interstitial lung disease (ILD) respectively ($p < 0.05$). CTD had a moderate effect on patient's QOL.

Conclusion: Photosensitivity was the commonest cutaneous manifestation among CTD patients. ANA was positive in the majority of SLE patients. The presence of anti-dsDNA was significantly associated with lupus nephritis, while anti-scl70 and ACA were strongly associated with systemic sclerosis and ILD. CTD had a moderate effect on patient's QOL.

KEYWORDS:
Clinical characteristics, connective tissue diseases, autoantibodies, quality of life, cutaneous manifestations, antinuclear antibodies

INTRODUCTION

Connective tissue diseases (CTDs) are defined as a group of complex chronic disorders with immune dysregulation that produces autoantibodies against their self-antigens.[1] CTDs include systemic lupus erythematosus (SLE), dermatomyositis or polymyositis, systemic sclerosis, Sjogren's syndrome, mixed connective tissue disease (MCTD) and overlap syndromes. The prevalence and incidence of each specific CTD varies geographically.[2]

CTDs can present with a heterogeneous clinical manifestation especially in the cutaneous system, ranging from non-specific cutaneous signs to disease-specific ones. The non-specific cutaneous signs include Raynaud's phenomenon, cutaneous vasculitis and livedo reticularis. The disease-specific cutaneous signs include discoid lupus erythematosus (DLE) and malar rash in SLE; Gottron's papule and heliotrope rash in dermatomyositis; as well as sclerodactyly, salt and pepper skin in systemic sclerosis.[3,4] Most CTDs have multiorgan involvement. The systemic manifestations of CTD like lupus nephritis in SLE and interstitial lung disease in systemic sclerosis can cause significant physical and functional impairment leading to poor quality of life (QOL).[5,6] Diagnosis of CTDs is usually based on a set of clinical and laboratory criteria. For instance, in SLE, diagnosis is based on the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria, which needs fulfilment of at least four criteria, with inclusion of at least one clinical and one immunological criterion. If lupus nephritis is present, it can be a sole clinical criterion with either antinuclear antibodies (ANA) or anti-double stranded DNA antibody (anti-dsDNA) positive. Certain CTDs require measurements of laboratory tests such as creatine kinase (CK) which could be elevated in patients with dermatomyositis or low complement levels in SLE. Some CTDs are difficult to diagnose at the first encounter and require time and elaborate investigations to reach an accurate diagnosis.[3,4] ANA and enucleated antibodies (ENA) play important role in establishing diagnosis, monitoring and prognosis evaluation in patients with CTDs.[7,8]

To date, there is a lack of studies looking into the cutaneous manifestations of CTD, their associations with autoantibodies, and their impact on QOL in Malaysia and Southeast Asia. This study aimed to describe the common cutaneous manifestations of CTDs in the local population, to determine the association with ANA and other associated antibodies and to assess the impact of CTDs on patient's QOL.

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MATERIALS AND METHODS

Study Design

This was a cross-sectional study conducted from March 2023 to June 2023 at Hospital Sultan Ismail Johor Bahru, the main tertiary referral centre for rheumatology in Johor, Malaysia. All patients aged 18 and above, with a confirmed diagnosis of SLE, systemic sclerosis, dermatomyositis, MCTD or overlap syndrome who attended the rheumatology clinic during the study period were recruited. The diagnosis of CTD was confirmed by qualified rheumatologists based on internationally accepted criteria - the 2012 SLICC criteria for SLE, the 2013 ACR/EULAR criteria for systemic sclerosis, the 2017 ACR/EULAR criteria for adult dermatomyositis, the Alarcon-Segovia criteria for MCTD and the presence of at least two autoimmune rheumatological diseases for overlap syndrome. Patients who did not fulfil diagnostic criteria for CTD and patients who refused to participate in the study were excluded.

Sample Size Estimation

Sample size estimation was calculated using the population proportion formula by Lenneshow, Hosmer, Klar, Lwanga & Organization 1990.[9] A minimum sample size of 75 subjects was needed to reject the null hypothesis with a power of 0.8. The type I error probability associated with this test for this null hypothesis was 0.05.

Study Procedures

A written consent was obtained from all patients who fulfilled the inclusion and exclusion criteria. History taking and physical examination were performed and recorded in the clinical report form (CRF). Information from the electronic medical record (EMR), including relevant rheumatology history and findings, as well as investigation results were retrieved from the EMR and recorded in CRF.

Dermatology Quality Life Index

All subjects were required to fill up a validated and licensed Dermatology Quality Life Index (DLQI) form. The DLQI stratifies the QOL into five categories-: no effect at all on the patient's life (0–1), a small effect on the patient's life (2–5), moderate effect on the patient's life (6–10), very large effect on the patient's life (11–20) and extremely large effect on the patient's life (21–30).[10]

Statistical Analysis

Statistical analysis was performed using the Statistical Package of the Social Science version 25 (SPSS, IBM Corporation, Chicago, IL, USA). Baseline characteristics were expressed as numbers and percentages or mean and standard deviation. Comparison of categorical variables for association with autoantibodies was done using the Chi-square test/Fisher's exact test. A p-value of less than 0.05 was considered statistically significant.

Ethical Approval

This study was approved by the Medical Research and Ethical Committee, Ministry of Health, Malaysia (NMRR-23-00222-0A5).

RESULTS

A total of 79 patients were recruited. The majority of patients were females, with a female-to-male ratio of 10:1. The mean age was 39± 14.5 years with mean age at diagnosis 30± 14.6 years. The mean duration of disease was 9.4± 7.3 years. Malay was the predominant ethnic group with 45 patients (57%). Out of the 79 CTD patients, SLE was the most common, 64 patients (81.0%), while MCTD was the least common, one patient (1.3%). SLE was present in all patients with MCTD and overlap syndrome. The baseline characteristics are listed in Table I.

The clinical features of CTD and the associated antibodies are shown in Table II. All patients had cutaneous involvement, with photosensitivity being the commonest manifestation (65 patients, 82.3%). As for systemic symptoms, the majority of patients had musculoskeletal involvement (66 patients, 83.5%).

The majority of SLE patients had photosensitivity, while Raynaud's phenomenon, poikiloderma and skin tightness were the commonest cutaneous manifestations seen in systemic sclerosis. Table III summarises the commonest cutaneous manifestation seen in each CTD.

The frequency of positive autoantibodies is shown in Table II. The majority of patients (75 patients, 94.9%) had positive ANA, while anti-SSA/Ro and anti-dsDNA antibodies were present in 40.5% and 39.2% of patients respectively.

ANA and anti-dsDNA positivity were significantly higher among SLE patients compared to other CTDs while anti-scl70 and anti-centromere antibodies (ACA) were strongly associated with patients with systemic sclerosis ($p < 0.05$). Anti-dsDNA was also significantly associated with renal involvement mainly lupus nephritis, while anti-scl70 was significantly associated with respiratory symptoms, mainly interstitial lung disease (ILD) ($p < 0.05$). The association between CTDs and autoantibodies is summarised in Table IV.

CTDs generally had a moderate effect on patients' quality of life, with a mean DLQI score of 6.42± 5.53. There were 16 patients with a DLQI score of more than 10, with the majority of them having SLE (81.3%) and systemic symptoms (93.8%). The DLQI score for each CTD is summarised in Table V.

DISCUSSION

CTDs are autoimmune multisystem disorders that commonly involve the skin and mucous membranes. Cutaneous involvement may be the earliest manifestation of CTD and thus, important for early recognition of CTD. Our study showed that patients with CTD were mostly females and of childbearing age, similar to previous studies[11,12] SLE was the commonest CTD in our cohort, similar to the findings by Kadiru et al and Jethwa et al.[11,13] Although there are limited studies done looking at the prevalence and incidence of CTDs in different ethnic groups, we found that CTDs were highest in our Malay population. Our finding was also similar to a study done by Ng et al[14] which suggests that genetics may play a role.

Table I: Baseline characteristics in 79 patients with CTD

Clinical characteristics	Number of patients (%), n = 79
Mean age ± SD, years	39 ± 14.5
Mean age at diagnosis ± SD, years	30 ± 14.6
Gender	
Female	72 (91.0)
Male	7 (8.9)
Ethnic group	
Malay	45 (57.0)
Chinese	30 (38.0)
Indian	4 (5.1)
Mean duration of disease ± SD, years	9.4 ± 7.3
Connective tissue disease	
SLE	64 (81.0)
Systemic sclerosis	6 (7.6)
Dermatomyositis	4 (5.1)
MCTD	1 (1.3)
Overlap syndrome	4 (5.1)

Table II: Clinical features and associated autoantibodies

Clinical features	Number of patients, n = 79	Percentage (%)
Cutaneous manifestations	79	100
Photosensitivity*	65	82.3
Non-scarring alopecia	64	81.0
Malar rash	53	67.0
Oral ulcer	44	55.7
Discoid rash	32	40.5
Raynaud's phenomena	32	40.5
Purpura	28	35.4
Livedo reticularis	13	16.5
Chronic urticaria	10	12.7
Gottron's papule	8	10.1
Systemic manifestations		
Musculoskeletal	66	83.5
Haematology	35	44.3
Renal	20	25.3
Respiratory	16	20.3
Gastrointestinal	13	16.5
Cardiovascular	13	16.5
Neurological	8	10.1
Autoantibodies positivity at baseline		
ANA	75	94.9
Anti-SSA/Ro	32	40.5
Anti-dsDNA	31	39.2
Anti-RNP	27	34.2
Anti-Sm	25	31.6
Anti-SSB/La	9	11.4
Anti-riboprotein	4	5.1
Anti-scl70	3	3.8
Anti-centromere (ACA)	3	3.8
Anti-histone	1	1.3
Anti-jo 1	1	1.3

*Photosensitivity = eczematous or morbilliform rash at the extensor of the arms, hands, upper chest and back upon exposure to sunlight.

Table III: The commonest cutaneous manifestation in each connective tissue disease

CTD	Cutaneous manifestation, n (%)
SLE	Photosensitivity*, 59 (92.2)
Dermatomyositis	Heliotrope rash, 3 (75.0)
MCTD	Heliotrope rash, Gottron papule, chronic urticaria, 1 (100.0)
Overlap syndrome	Non- scarring alopecia, 4 (100.0)
Systemic sclerosis	Raynaud's phenomenon, poikiloderma, skin tightness, 5 (83.3)

*Photosensitivity = eczematous or morbilliform rash at the extensor of the arms, hands, upper chest and back upon exposure to sunlight

Table IV: Association between connective tissue diseases and autoantibodies

		Anti-dsDNA[b], n(%)		p value	ANA[a], n(%)		p value
		Present	Absent		Present	Absent	
SLE	Present	29(45.3)	35(54.7)	*0.02	63(98.4)	1(1.6)	*0.02
	Absent	2 (13.3)	13(86.7)		12(80)	3(20)	
Renal system involvement	Present	12(60)	8(40)	*0.03			
	Absent	19(32.2)	40(67.8)				
		Anti-scl70[a], n(%)		p value	ANA[a], n(%)		p value
		Present	Absent		Present	Absent	
Systemic sclerosis	Present	3(50)	3(50)	*0.00	2(33.3)	4(66.7)	*0.01
	Absent	0	73(100)		1(1.4)	72(98.6)	
Respiratory system involvement	Present	3(18.8)	13(81.3)	*0.007			
	Absent	0	63(81.3)				

[a]Fisher exact test
bPearson Chi-square
*p < 0.05

Table V: DLQI Scores for each CTD

Type of CTDs	DLQI<10 (63), n(%)	DLQI≥10 (16), n(%)
SLE	51 (80.9)	13 (81.3)
Systemic sclerosis	5 (7.9)	1 (6.3)
Dermatomyositis	3 (4.8)	1 (6.3)
Overlap syndrome	3 (4.8)	1 (6.3)
MCTD	1 (1.6)	0

DLQI: Dermatology life quality index
MCTD: Mixed connective tissue disease

Photosensitivity was the commonest cutaneous manifestation detected among our CTD patients and was present in almost all SLE patients. This finding was similarly reported by Jethwa et al.[13] Therefore the presence of photosensitivity should prompt the clinician to have a high index of suspicion for CTDs, especially SLE.

Autoantibodies are important in the diagnosis of CTD.[15–17] ANA can be detected with elevated titters usually ≥ 1:160 in CTDs, compared to the general population due to the method of detection of ANA by using indirect immunofluorescence assay.[18,19] ANA was the commonest autoantibody detected and was present in the majority of our SLE patients. This finding is consistent with its high sensitivity and specificity for SLE.[15,19,20] A negative ANA test may therefore suggest an alternative diagnosis for the patient.

Anti-dsDNA positivity in our SLE patients was significantly associated with the presence of lupus nephritis. Previous studies showed that anti-dsDNA was detected in 63–68% of patients with lupus nephritis, similarly to our current finding.[21,22] Therefore, a positive anti-dsDNA may prompt clinicians to be more vigilant in detecting renal involvement among SLE patients. Early detection of lupus nephritis is important for the initiation of treatment to prevent the progression of renal involvement in SLE.

In our study, the presence of anti-scl70 and ACA were significantly associated with systemic sclerosis and ILD. This association was also similarly seen in previous studies.[23–25] Therefore, screening for these antibodies is important to prognosticate patients with systemic sclerosis. Early referrals to rheumatology and pulmonology colleagues are vital so that early immunosuppressive therapy can be given to halt disease progression.

Many previous studies have shown that the QOL of patients with CTD was significantly affected in comparison to the general population.[26–28] The mean DLQI in our patients was 6.42 ± 5.53, indicating a moderate effect on their QOL. A study conducted by Trepanowski et al.[29] also showed that CTD patients were moderately affected by their disease. This similar DLQI was also seen in other chronic inflammatory skin conditions like psoriasis.[30] Therefore, appropriate support and counselling should be offered to CTD patients to help them in coping with their chronic condition.

CONCLUSION

This study showed that photosensitivity was the commonest cutaneous manifestation seen among patients with connective tissue diseases (CTDs), especially systemic lupus erythematosus (SLE). Antinuclear antibody (ANA) was positive in almost all SLE patients. The presence of anti-dsDNA was significantly associated with lupus nephritis, while anti-scl70 and anti-centromere antibodies (ACA) positivity were significantly associated with systemic sclerosis. Anti-scl70 was also strongly associated with interstitial lung disease (ILD). Most patients with CTD were moderately affected by their disease. These findings highlight the important cutaneous features to recognise in aiding in the early diagnosis of CTDs. The presence of autoantibodies can guide physicians in the diagnosis of CTDs, detection of systemic involvement and initiation of effective treatment to reduce morbidity and improve patient's quality of life.

LIMITATIONS

Limitations of this study include small sample size and short duration of study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No: ..... **Date:** .....

Name: ..... **Score:** .....

Address: ..... **Diagnosis:** .....

.....

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐		
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐		
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
6.	Over the last week, how much has your skin made it difficultfor you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant	☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐		
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making yourhome messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐

DERMATOLOGY LIFE QUALITY INDEX (DLQI) - INSTRUCTIONS FOR USE

The Dermatology Life Quality Index questionnaire is designed for use in adults, i.e. patients over the age of 16. It is self explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one or two minutes.

SCORING

The scoring of each question is as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question 7, 'prevented work or studying'	scored 3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

HOW TO INTERPRET MEANING OF DLQI SCORES

0 – 1	no effect at all on patient's life2
– 5	small effect on patient's life
6 – 10	moderate effect on patient's life
11 – 20	very large effect on patient's life
21 – 30	extremely large effect on patient's life

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