Direct Immunofluorescence in Cutaneous and Systemic Lupus Erythematosus: A Literature Review

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ABSTRACT

Cutaneous manifestations of lupus erythematosus (LE) have a variety of clinical phenotypes and require proper investigation for diagnosis. Knowledge of the direct immunofluorescence (DIF) technique has improved and played an important role in the diagnosis of cutaneous LE. This review explores and summarizes reported DIF findings of each cutaneous LE variant. Historically, DIF findings of cutaneous LE have revealed deposits of multiple immunoreactants at the dermo-epidermal junction with either linear or granular patterns. Immunoglobulin M is the most common immunoreactant and DIF findings of cutaneous LE variants overlap. Therefore, diagnosis of cutaneous LE requires a combination of monitoring patient history, physical examinations and laboratory studies. This review helps interpret and better understand the application of DIF studies in cutaneous LE.

Keywords: Direct immunofluorescence; Lupus erythematosus (Siriraj Med J 2023; 75: 145-166)

Abbreviations

ACLE: acute cutaneous lupus erythematosus
ANA: antinuclear antibodies
BSLE: bullous systemic lupus erythematosus
CCLE: chronic cutaneous lupus erythematosus
C: complement
CB: cytoid bodies
DEJ: dermo-epidermal junction
DIF: direct immunofluorescence study
DLE: discoid lupus erythematosus
DLP: dust-like particles
DNA: Deoxyribonucleic acid
ENS: epidermal nuclear staining
Ig: immunoglobulin
LB: lupus band
LE: lupus erythematosus
NLE: neonatal lupus erythematosus
SCLE: subacute cutaneous lupus erythematosus
SLE: systemic lupus erythematosus
TEN: toxic epidermal necrolysis

INTRODUCTION

Lupus erythematosus (LE) is an autoimmune disease involving multiple organs such as the skin, musculoskeletal system, kidneys, and hematologic involvement. It predominantly affects young women aged 20-40. Cutaneous presentations can vary and is found in 59%-85% of patients. Cutaneous LE is categorized into two groups; (i) LE-specific skin rash and (ii) LE-nonspecific skin rash.[1] There are three subsets of LE-specific skin rash known as acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE), and chronic cutaneous LE (CCLE).[2] LE-nonspecific skin rashes have various presentations such as vasculitis, periungual telangiectasia, non-scarring alopecia, calcinosis cutis, urticaria, and erythromelalgia.

ACLE lesions occur as localized (malar rash) or generalized distributions (lupus maculopapular rash, photosensitive lupus dermatitis, and toxic epidermal necrolysis-like). Meanwhile, SCLE presents itself as

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papulosquamous (psoriasiform) SCLE or annular polycyclic SCLE. CCLE is the most common form of cutaneous LE and is often found as discoid lupus erythematosus (DLE). Other variants of CCLE include tumid LE, lupus panniculitis/lupus profundus, hypertrophic/verrucous DLE, mucosal LE, oral DLE, conjunctival DLE, lichenoid DLE and chilblain LE.[3] Of the three subtypes of LE-specific sin rash, ACLE is generally associated with systemic involvement and is parallel with underlying SLE disease activity (90%), followed by SCLE (33%).[4,5] CCLE rarely progresses to systemic involvement (5%).[6]

Generally, LE can be diagnosed by studying patient history, clinical presentations (skin and other organ involvement), and serology. A skin biopsy for histopathology examination and a direct immunofluorescence (DIF) test are helpful in detecting unusual or atypical presentations. Basal layer degeneration (interface dermatitis) with mucin deposition and infiltration of mononuclear cells at the perivascular and peri-appendage are hallmark signs of LE. However, these histological findings differ among cutaneous LE subtypes and are also found in other connective tissue diseases. In those cases, DIF is helpful in providing a more precise diagnosis.[7] Thus, this article aims to review DIF findings among different LE-skin rash subtypes. The literature was searched in electronic database (PubMed) using the terms of "cutaneous lupus erythematosus", "oral lupus erythematosus", "systemic lupus erythematosus" and "direct immunofluorescence" through June 2022.

DIF tests

The immunofluorescence technique was developed in the 1940s by Coons.[8] DIF reveals tissue-bound autoantibodies in tissues or cells.[8] In 1963, the technique was introduced to dermatology, leading to the discovery of immunoreactants along the dermo-epidermal junction (DEJ), which are also known as lupus bands (LB)[9] (Fig 1A). A suitable skin biopsy site is determined by the suspected disease. In cutaneous LE, biopsies should be performed at active lesion areas, which are often exposed to the sun, because deposits of immune complex usually present in lesion skin.[10] Occasionally, DIF tests in LE patients also reveal positive LB in non-lesion and non-sun exposed areas.[11] Established lesions with longer durations (one to six months) can provide higher positive yields (80%) than lesions that are less than one month old (30%).[10,12]

In a DIF test, skin biopsy specimens should either be quick frozen or put in Michel's transport medium for subsequent quick freezing. Michel's transport medium can store skin biopsy specimens for up to four weeks at 4-8°C. During this process, a frozen tissue is inserted in a resin on a cooled metal chunk in the cryostat and each section is cut into 4-5 μm.[8] The sections are then placed and dried on a slide for staining. The immunoreactants, including immunoglobulin IgG IgM, IgA, complement C3 and/or fibrinogen are put into each slide.[8] Each slide is covered by a glass cover slide and interpreted under immunofluorescence microscopy.[8] The types of immunoreactants, sites, and patterns of depositions are evaluated and interpreted for diagnosis.

Various DIF results have been noted in LE. Generally, deposits of multiple immunoreactants along the DEJ are the most reported pattern (approximately 80%).[13,14] Among immunodeposits at the DEJ, IgM is the most common.[15] However, IgG deposit at the DEJ of involved skin are more specific than IgM. IgG deposits in the nucleus of keratinocytes known as epidermal nuclear staining (ENS) or *in vivo* antinuclear antibodies (ANA) are generally

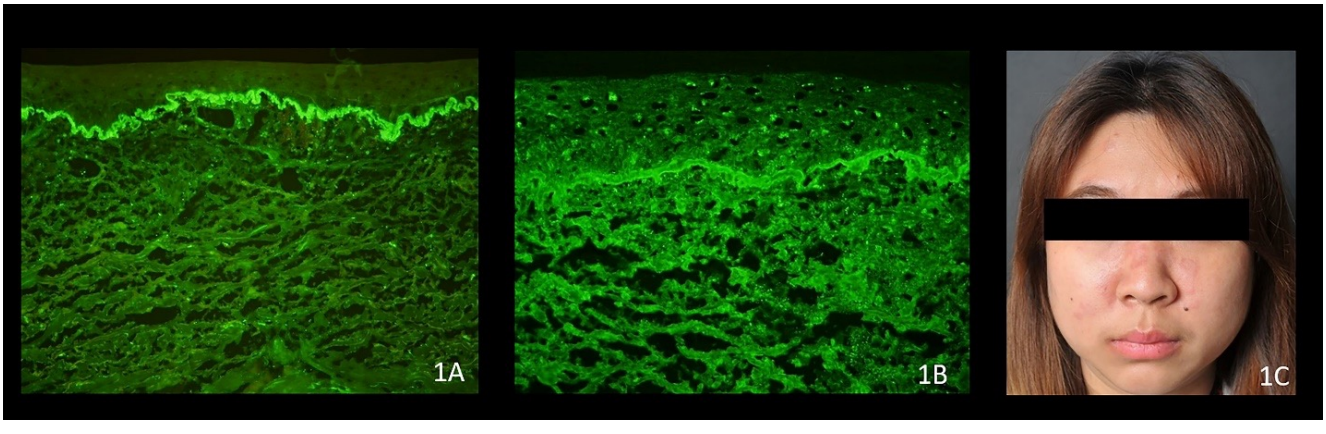

Fig 1A. Direct immunofluorescence (DIF) findings of cutaneous lupus erythematosus showing positive homogenous deposits of immunoglobulin (Ig)M at the dermo-epidermal junction (DEJ) were recognized as lupus bands. (10x magnification).
Fig 1B. DIF findings of acute cutaneous lupus erythematosus showed positive epidermal nuclear staining of IgG. (20x magnification).
Fig 1C. Clinical presentation of acute cutaneous lupus erythematosus showed ill-defined erythematous plaque localized on both cheeks and nose.

found more often than other connective tissue diseases. Dust-like particles (DLP) are defined as patchy deposits of tiny granules which appear as fine speckle patterns or technical artifacts. They can be found on the basal layer of the epidermis (intercellular and intracellular areas), DEJ, or the upper part of the dermis.[16] DLP is specific for SCLE.[16-19] Deposits of immunoreactants along blood vessels, periadnexal areas, and cytoid bodies (CB) have also been observed.[14]

DIF test of systemic lupus erythematosus (Table 1)

Based on our review, some studies investigated DIF results of cutaneous lesions in systemic lupus erythematosus (SLE) patients without identifying the type of lesion. There was a positive result in 42%-100% lesion cases, and 32%-92.9% in non-lesion cases.[7,16,20-28] The pattern of immunodeposition at the DEJ was homogenous, thready, strippled, granular, and linear. A homogenous pattern was defined as a thick, solid, well-demarcated, continued line at the DEJ. The thready pattern was defined as short, close-set threads or fibrils, sometimes with a long axis at right angles to the DEJ. Last but not least, the stippled pattern was defined as a discontinuous broken line with multiple small round points of fluorescence. The common pattern and immunodeposits at the DEJ were granular and IgM, respectively.[20,23,29]

DIF tests of LE-specific skin lesions (Table 1)

Acute cutaneous lupus erythematosus

ACLE typically presents itself as symmetrical papules confluent to plaques in photosensitive areas such as malar eminence, the forehead, V-neck, and extensor arms. (Fig 1C) ACLE lesions can persist for days to weeks. In cases of intense inflammation, some patients suffer from atypical target lesions or epidermal detachment called Stevens-Johnson syndrome or toxic epidermal necrolysis (TEN)-like pattern.[15] A positive DIF result in ACLE depends on the site of the skin biopsy. Positive results in lesion skin ranges from 60%-100% and is 25% in non-lesion skin.[13,14,13-15,25,30] Multiple immunodeposits at the DEJ was the most common DIF finding. TEN-like ACLE also exhibited immunodeposits at the DEJ.[15] ENS was positive in 47.1% of all ACLE lesions[14] (Fig 1B). Fluorescent CB in the papillary dermis, immunoreactants in the blood vessels or periadnexal areas with granular pattern were also observed.[14]

Subacute lupus erythematosus

SCLE frequently presents itself as non-scarring or non-atrophic symmetrical erythematous macules or papules. It is predominantly distributed in photosensitive areas such as the face, anterior and posterior neck or extensor arms. Other variants include drug-induced SCLE and neonatal lupus erythematosus (NLE). SCLE is associated with positive Ro/SSA antibodies.[31] The positive yields in lesion skin (34%-100%) and non-lesion skin (36%-100%) of SCLE were equal.[14,16-19,22,32-37] Deposits of various immunoreactants along the DEJ with granular pattern was common, followed by DLP staining in the epidermis, and subepidermal region.[16-19,22,25,33,35-38] As previously mentioned, DLP is associated with SCLE. Under experimental control, DLP was initially detected within two weeks after artificial light exposure.[16] A previous study showed that DLP was highly specific for SCLE, but its sensitivity was low (30%). There was no significant relation between the presence of DLP and anti-SSA/Ro antibodies, and ANA.[18] Furthermore, patterns of DIF findings were not associated with systemic involvements in SCLE.[33] IgG and IgM were detected most at the DEJ in SCLE, followed by IgA and C3.

In the case of drug-induced SCLE and NLE, DIF findings showed similar results to idiopathic SCLE.[39] Transfer of anti-RSSA/Ro and/or anti-SSB/La from the mother to fetus via the placenta also induced NLE. Annular erythematous plaques on the face and scalp are a hallmark of NLE. Data regarding DIF findings of NLE is limited as we found only one study reporting on it.[39]

Chronic cutaneous lupus erythematosus

Discoid lupus erythematosus

DLE is described by well-defined indurated erythematous coin-shaped plaques coated by adherent scales with keratotic spikes (carpet tack sign). The lesions slowly progress to an atrophic scarring center with an active erythema periphery. DLE lesions can occur in both sun-exposed areas such as the face, ears, upper chest or extensor surface of extremities and sun-protected areas such as the scalp or trunk. Scarring alopecia is usually observed in DLE (Fig 2C).

DIF tests have also revealed deposits of multiple immunoreactants along the DEJ with granular patterns that extend to the basement membrane of hair follicles or peri-appendage areas (Fig 2A & 2B). The positive yield ranges from 27.2%-100% in lesion areas and 45.5%-69.2% in non-lesion areas.[14,16,22,23,33,35,40-48] ENS has also been found, but at a lower frequency than ACLE and SCLE. DIF tests of oral DLE lesions have also revealed deposits of multiple immunoglobulins at the DEJ with either granular or homogeneous bands, similar to DLE lesions on glabrous skin.[43] Deposits of fibrinogen at the DEJ extending into the upper dermis has also been reported in oral DLE, however, the depth and thickness

TABLE 1. Literature review of direct immunofluorescence findings in cutaneous lupus erythematosus.

Systemic lupus erythematous							
Study	**Ethnicity**	**Positive DIF (%)**	**Site of skin biopsy**	**DIF findings**			
				Epidermis	**DEJ**		**Others**
					Pattern	**Immunoreactants**	
Tay et al.[24] (1975)	Asian (Singapore)	41%	Lesion	-	(i) Homogenous (63%)	IgM (85.5%) IgG (71.2%) C3 (57.1%) IgA (28.5%)	-
					(ii) Thready (26.8%)	Fibrinogen (14.2%) IgM (100%) IgG (70%)	
		32%	Non-lesion	-	(iii) Stippled (10%)	IgA (30%) C3 (20%) fibrinogen (10%)	-
Dantzig et al.[29] (1975)	Caucasian (United States)	13/24 (54%)	Non-lesion (Sun-protected area)	-	N/A (100%)	IgG (84.6%) IgM (84.6%) C3 (30.8%)	-
Gammon et al.[20] (1983)	Caucasian (United States)	4/4 (100%)	Lesion	-	(i) Stippled (N/A)	IgG (100%) IgA (75%) IgM (25%) C3 (25%)	-
		10/11 (90.9%)	Non-lesion (Sun-exposed area)		(ii) Granular (N/A)	IgG (90%) IgM (50%) IgA (50%) C3 (40%)	-
		13/14 (92.9%)	Non-lesion (Sun-protected area)		(iii) Homogeneous (N/A)	IgG (92.3%) IgA (53.8%) IgM (38.5%) C3 (38.5%)	-
Magro et al.[22] (1997)	Caucasian (England, Canada)	7/7 (100%)	Lesion	-	N/A (100%)	IgM (100%) IgG (70%) C3 (40%) IgA (30%)	
		4/4 (100%)	Lesion (Sun-protected area)	ENS[φ] (40%)	-	-	Positive immunoreactants at cytoplasm decoration of keratinocytes (10%)

TABLE 1. Literature review of direct immunofluorescence findings in cutaneous lupus erythematosus. (Continued)

Systemic lupus erythematous							
Study	**Ethnicity**	**Positive DIF (%)**	**Site of skin biopsy**	**DIF findings**			
				Epidermis	**DEJ**		**Others**
					Pattern	**Immunoreactants**	
Nyberg et al.[16] (1998)	Caucasian (Sweden)	1/1 (100%)	Lesion	-	Linear (100%)	IgM (100%)	-
Minz et al.[23] (2010)	Asian (India)	10/14 (71.4%)	Lesion	-	Granular (100%)	IgM (93.3%) IgG (67%) C3 (60%) IgA (33%)	Positive immunoreactants at BV (40%)
Brinster et al.[26] (2012)	Caucasian (United States)	2/4 (50%)	Lesion	-	Granular (100%)	IgG, IgM, C3	-
Luo et al.[21] (2013)	Asian (China)	28/28 (100%)	Lesion	-	(i) Homogenous (N/A) (ii) Granular (N/A)	IgM (86%) C3 (55.6%) IgG (25%) IgA (22%)	-
Abreu Velez et al.[7] (2016)	Caucasian (United States)	5/5 (100%)	Lesion	-	N/A (100%)	IgG, IgM, IgA, C3, C1q, fibrinogen	Positive immunoreactants at basement membranes of eccrine gland and sebaceous gland (N/A)
Elbendary et al.[28] (2016)	Caucasian (United States)	100/100 (100%)	Lesion	-	Granular (100%)	IgM (89%) IgG (76%) C3 (73%) IgA (60%)	Positive immunoreactants at stromal-epithelial junction of hair follicle and sweat gland apparatus in granular pattern (100%)
Chanprapaph et al.[27] (2019)	Asian (Thailand)	25/32 (78.1%)	Lesion	ENS (24%)	Homogenous granular (100%)	IgM (76%) C3 (48%) IgG (40%) IgA (16%)	Positive immunoreactants at follicular epithelium (100%) CB (44%), peri-eccrine area (24%) and peri-sebaceous staining (16%)

TABLE 1. Literature review of direct immunofluorescence findings in cutaneous lupus erythematosus. (Continued)

Acute cutaneous lupus erythematosus							
Study	**Ethnicity**	**Positive DIF (%)**	**Site of skin biopsy**	**DIF findings**			**Others**
				Epidermis	**DEJ**		
					Pattern	**Immunoreactants**	
Weinstein et al.[25] (1987)	- (Australia)	3/5 (60%)	Lesion (100%)	-	Granular	IgG, IgM, IgA, C3, and/or Clq	-
Ng et al.[13] (2000)	Asian (Singapore)	16/20 (80%)	Lesion	-	Homogenous Granular (100%)	C1q (94%) IgG (75%) IgM (69%) C3 (50%)	-
		1/4 (25%)	Non-lesion	-	Granular (100%)	N/A	-
Abdelmouttalib et al.[15] (2021)	Arab (Morocco)	2/2 (100%)	Lesion (TEN-like LE)	-	Granular (100%)	IgM (100%) IgG (50%) C3 (50%)	-
Roberts et al.[30] (2021)	Caucasian (England)	1/1 (100%)	Lesion	-	Linear (100%)	IgG, IgA, IgM, C3	-
Chanprapaph et al.[14] (2021)	Asian (Thailand)	17/21 (81%)	Lesion	ENS (47.1%)	Homogenous Granular (76.5%)	N/A	Positive immunoreactants at CB (70.6%), BV (35.3%), peri-follicular area (17.6%) and peri-eccrine area (5.9%)
Subacute cutaneous lupus erythematosus							
Study	**Ethnicity**	**Positive DIF (%)**	**Site of skin biopsy**	**DIF findings**			**Others**
				Epidermis	**DEJ**		
					Pattern	**Immunoreactants**	
Nieboer et al.[18] (1988)	Caucasian (Netherlands)	12/35 (34%)	Lesion	DLP (100%)	DLP (100%)	IgG (100%)	Positive IgG at dermis in DLP pattern (100%)
David-Bajar et al.[33] (1992)	- (United States)	7/7 (100%)	Lesion	N/A	N/A	IgM (100%) C3b (71.4%)	-
		7/7 (100%)	Non-lesion (Sun-exposed and sun-protected area)	N/A (14.3%)	N/A (100%)	IgG (100%)	-

TABLE 1. Literature review of direct immunofluorescence findings in cutaneous lupus erythematosus. (Continued)

Subacute cutaneous lupus erythematosus							
Study	**Ethnicity**	**Positive DIF (%)**	**Site of skin biopsy**	**DIF findings**			
				Epidermis	**DEJ**		**Others**
					Pattern	**Immunoreactants**	
Valeski et al.[19] (1992)	- (United States)	32/32 (100%)	Lesion	DLP[δ] (100%)	Speckle (100%)	IgG (100%) IgM (25%) IgA (9.4%)	Positive immunoreactants at ductal and/or follicular epithelium (N/A)
Crowson et al.[32] (1997)	Caucasian (England, Canada)	6/6 (100%)	Lesion	(i) Granular (Nucleus and cytoplasm, 16.7%) (ii) Peripheral homogeneous (Nucleus, 33.3%) (iii) Granular (Nuclear, 16.7%) (iv) Peculiar (Intercellular space of epithelial cells, 16.7%)	Granular (50%)	IgM (100%)	-
Magro et al.[22] (1997)	Caucasian (England, Canada)	10/10 (100%)	Lesion	ENS (100%)	N/A (100%)	IgM (85.7%) IgG (14.3%) IgA (14.3%) C3 (14.3%)	Positive IgG at cytoplasm decoration of keratinocytes (60%)
Nyberg et al.[16] (1998)	Caucasian (Sweden)	1/2 (50%)	Lesion	-	DLP (50%)	IgG (100%)	Positive IgG at subepidermal area (50%)
			Non-lesion	-	DLP (50%)	C1q (100%)	Positive C1q at subepidermal area (50%)
Parodi et al.[36] (2000)	Caucasian (Italy)	50/58 (86%)	Lesion	DLP (6%)	N/A (100%)	IgA (52%) IgG (48%) IgM (48%)	-
		26/58 (44%)	Non-lesion (Sun-exposed area)	-	N/A (100%)	N/A	-
		21/58 (36%)	Non-lesion (Sun-protected area)	-	N/A (100%)	N/A	-

TABLE 1. Literature review of direct immunofluorescence findings in cutaneous lupus erythematosus. (Continued)

Subacute cutaneous lupus erythematosus							
Study	**Ethnicity**	**Positive DIF (%)**	**Site of skin biopsy**	**Epidermis**	**DIF findings DEJ**		**Others**
					Pattern	**Immunoreactants**	
Mutasim et al.[34] (2003)	Caucasian (United States)	1/1 (100%)	Lesion	Granular[ω] (100%)	N/A (100%)	Fibrinogen (100%)	-
Suess et al.[37] (2008)	Caucasian (Germany)	2/2 (100%)	Lesion	-	Focal granular (100%)	IgM (100%) C3 (50%)	-
			Non-lesion	-	(i) Linear (100%) (ii) Intermittent granular (100%)	IgA (100%) IgG (100%) IgM (100%) C3 (100%)	-
Marzano et al.[17] (2011)	Caucasian (Italy)	5/8 (62.5%)	Lesion (Sun-exposed area)	DLP (100%)	Granular (100%)	IgG ± IgM (100%) C3 (50%)	-
Mysorekar et al.[35] (2015)	Asian (India)	4/4 (100%)	Lesion	-	Granular (100%)	IgG (100%) IgA (100%) C3 (100%) IgM (75%)	-
Chanprapaph et al.[27] (2021)	Asian (Thailand)	5/7 (71.4%)	Lesion	ENS (20%)	Homogenous granular (20%)	N/A	Positive immunoreactants at CB (20%), BV (80%), and peri-eccrine area (40%)
Neonatal lupus erythematosus							
Study	**Ethnicity**	**Positive DIF (%)**	**Site of skin biopsy**	**Epidermis**	**DIF findings DEJ**		**Others**
					Pattern	**Immunoreactants**	
Maynard et al.[39] (1991)	- (United States)	2/3 (66.7%)	Lesion	ENS (100%)	Linear (50%)	IgM (100%)	Positive fibrinogen, IgM and C3 at superficial and mid-dermal BV (100%)

TABLE 1. Literature review of direct immunofluorescence findings in cutaneous lupus erythematosus. (Continued)

Chronic cutaneous lupus erythematosus							
Discoid lupus erythematosus							
Study	Ethnicity	Positive DIF (%)	Site of skin biopsy	DIF findings Epidermis	DEJ Pattern	DEJ Immunoreactants	Others
Schiodt et al.[43] (1981)	- (United States)	45/45 (100%)	Lesion (oral)	-	(i) Granular (N/A) (ii) Homogenous (N/A)	C3 (84%) Fibrinogen (89%) IgM (64%) IgA (27%) IgG (24%)	Positive immunoreactants at CB (N/A)
Weinstein et al.[25] (1987)	- (Australia)	5/9 (55%)	Lesion	-	Granular (100%)	IgG, IgM, IgA, C3, and/or Clq	-
David-Bajar et al.[33] (1992)	- (America)	8/11 (72.7%)	Lesion	-	Granular (100%)	C3 (100%) IgM (72.7%) IgA (36.4%) IgG (18.2%) IgG and C3 (60%)	-
		5/11 (45.5%)	Non-lesion	-	Granular (100%)	IgA (20%) IgM (20%)	-
Sugai et al.[48] (1992)	Latin America (Brazil)	47/71 (66.2%)	Lesion	-	(i) Granular (93.6%) (ii) Homogenous (70.2%) (iii) Thready (55.3%)	IgG (76.6%) IgM (61.7%) C3 (57.5%) IgA (25.5%)	-
Al-suwaid et al.[47] (1995)	Arab (Oman)	72.7%	Lesion	-	(i) Homogenous (55.5%) (ii) Granular (55.5%)	IgG (77.8%) C3 (44.4%) IgM (38.9%) IgA (22.2%)	-
Kulthanan et al.[48] (1996)	Asian (Thailand)	90/100 (90%)	Lesion	ENS (Speckle, 2%)	Granular (90%)	IgG (63%) C3 (50%) IgM (47%) IgA (22%)	Positive immunoreactants at CB (34%) and BV (15%)
Magro et al.[22] (1997)	Caucasian (England, Canada)	10/10 (100%)	Lesion	ENS (20%)	N/A (100%)	IgM (90%) IgG (70%) C3 (30%) IgA (20%)	-

TABLE 1. Literature review of direct immunofluorescence findings in cutaneous lupus erythematosus. (Continued)

Chronic cutaneous lupus erythematosus							
Discoid lupus erythematosus							
Study	**Ethnicity**	**Positive DIF (%)**	**Site of skin biopsy**	**DIF findings**			**Others**
				Epidermis	**DEJ**		
					Pattern	**Immunoreactants**	
Nyberg et al.[16] (1998)	Caucasian (Sweden)	9/13 (69.2%)	Lesion	-	(i) DLP (ii) Linear (Total 23.1%)	IgM (100%) C1q (83.3%) IgG (33.3%) C3 (33.3%)	Positive immunoreactants at DEJ and subepidermal area (46.2%)
			Non-lesion	-	(i) DLP (ii) Linear (Total 18.2%)	IgM (100%) IgG (75%) C1q (50%)	Positive immunoreactants at DEJ and subepidermal area (36.4%)
Badri et al.[40] (2005)	Arab (Tunisia)	1/1 (100%)	Lesion	-	Granular (100%)	IgM (100%)	-
Serpico et al.[44] (2007)	Caucasian (Italy)	1/1 (100%)	Lesion	-	Linear (100%)	IgG, IgA, fibrinogen	-
Chularojanamontri et al.[41] (2010)	Asian (Thailand)	33/61 (54.1%)	Lesion	-	N/A (100%)	IgM (82%) IgA (34.4%) C3 (31.1%) IgG (14.8%)	Positive immunoreactants at CB (100%)
Minz et al.[23] (2010)	Asian (India)	13/22 (59.1%)	Lesion	-	Granular (100%)	IgM (93.3%) IgG (67%) C3 (60%) IgA (33%)	Positive immunoreactants at BV (26.7%)
Mysorekar et al.[35] (2015)	Asian (India)	2/2 (100%)	Lesion	-	Granular (100%)	IgG (100%) IgA (100%) C3 (100%) IgM (50%)	-
Ohata et al.[46] (2016)	Asian (Japan)	-	Lesion	-	N/A	IgM (100%) C3 (88.9%) IgG (66.7%) IgA (66.7%)	-
Chanprapaph et al.[14] (2021)	Asian (Thailand)	22/81 (27.2%)	Lesion	ENS (13.6%)	Homogenous granular (68.2%)	N/A	Positive immunoreactants at CB (50%), BV (41%), peri-follicular area (27.3%) and peri-eccrine area (54.5%)

TABLE 1. Literature review of direct immunofluorescence findings in cutaneous lupus erythematosus. (Continued)

Lupus panniculitis							
Study	**Ethnicity**	**Positive DIF (%)**	**Site of skin biopsy**	**DIF findings**			**Others**
				Epidermis	**DEJ**		
					Pattern	**Immunoreactants**	
Tuffanelli et al.[51] (1971)	- (United States)	4/6 (66.7%)	Lesion	-	N/A (100%)	IgG, IgM, C3	-
Sanchez et al.[49] (1981)	- (United States)	12/17 (70.6%)	Lesion	-	N/A (100%)	IgM (100%) C3 (50%) Fibrin (16.7%) IgA (8.3%)	Positive immunoreactants at BV (25%) and CB (8.3%)
Izumi et al.[50] (1983)	- (United States)	1/1 (100%)	Lesion	-	Linear (100%)	IgG, C3	Positive immunoreactants at follicular epithelium (100%)
Lupus erythematosus tumidus							
Study	**Ethnicity**	**Positive DIF (%)**	**Site of skin biopsy**	**DIF findings**			**Others**
				Epidermis	**DEJ**		
					Pattern	**Immunoreactants**	
Bouzit et al.[54] (1999)	Caucasian (France)	1/1 (100%)	Lesion	-	Granular (100%)	IgM (100%)	-
Alexiades-Armenakas et al.[52] (2003)	- (United States)	5/10 (50%)	Lesion	-	(i) Linear (100%) (ii) Granular (80%)	IgM (100%) IgG (80%) IgA (20%) C3 (20%) Fibrin (20%)	-
Vieira et al.[53] (2006)	Caucasian (Spain)	4/15 (26.7%)	Lesion	-	N/A (100%)	IgG (75%) C3 (50%) IgM (25%) C1q (25%)	-
Hashimoto et al.[55] (2017)	Asian (Japan)	1/1 (100%)	Lesion	-	Linear (100%)	IgG, C3	-

TABLE 1. Literature review of direct immunofluorescence findings in cutaneous lupus erythematosus. (Continued)

Study	Ethnicity	Positive DIF (%)	Site of skin biopsy	DIF findings: Epidermis	DIF findings: DEJ Pattern	DIF findings: DEJ Immunoreactants	Others
Chilblain lupus erythematosus							
Pock et al.[56] (2001)	Caucasian (Czech Republic)	1/1 (100%)	Lesion	-	(i) Granular (100%) (ii) Tatter-like and globular (100%)	IgG, IgA, IgM, C3 Fibrinogen	Positive immunoreactants at dermis (papillary dermis) in globular pattern (100%)
Patel et al.[57] (2013)	Caucasian (United Kingdom)	1/1 (100%)	Lesion	-	-	-	Positive fibrin at BV (100%)
Hypertrophic/verrucous lupus erythematosus							
Khorshid et al.[58] (1999)	Caucasian (United Kingdom)	1/1 (100%)	Lesion	ENS (Speckle,100%)	Linear (100%)	IgG, IgM and C3	Positive immunoreactants at superficial dermal BV (100%)
Non-specific lupus cutaneous manifestations							
Bullous systemic lupus erythematosus							
Olansky et al.[71] (1982)	Caucasian (United States)	2/2 (100%)	N/A	-	Linear (100%)	IgG, C3	-
Camisa et al.[65] (1983)	Caucasian (United States)	2/2 (100%)	Peri-lesion	-	Granular (100%)	IgG (100%) IgM (100%) IgA (50%)	-
Janniger et al.[68] (1991)	Caucasian (Poland)	1/1 (100%)	Peri-lesion	-	Linear and granular (100%)	IgG, IgM, C3	-
Shirahama et al.[72] (1994)	Asian (Japan)	1/1 (100%)	N/A	-	N/A (100%)	IgG, IgM, IgA	-

TABLE 1. Literature review of direct immunofluorescence findings in cutaneous lupus erythematosus. (Continued)

Non-specific lupus cutaneous manifestations							
Bullous systemic lupus erythematosus							
Study	Ethnicity	Positive DIF (%)	Site of skin biopsy	DIF findings			Others
				Epidermis	DEJ		
					Pattern	Immunoreactants	
Yell et al.[59] (1995)	Caucasian (United Kingdom)	6/7 (85.7%)	Peri-lesion	-	(i) Linear (83.3%) (ii) Granular (16.7%)	IgG (83.3%) IgM (83.3%) IgA (83.3%) C3 (83.3%)	-
Yung et al.[74] (2000)	Caucasian (New Zealand)	1/1 (100%)	N/A	-	Granular (100%)	IgG, IgA, IgM, complement	-
Nitta et al.[70] (2002)	Asian (Japan)	1/1 (100%)	Peri-lesion	-	Linear and granular	IgG, IgA, IgM, C3	-
Barbosa et al.[71] (2011)	Latin America (Brazil)	1/1 (100%)	N/A	-	N/A	IgG, IgA, fibrin	-
Miziara et al.[69] (2013)	Latin America (Brazil)	1/1 (100%)	Lesion	-	Linear (100%)	IgG, IgM, IgA	-
Mysorekar et al.[35] (2015)	Asian (India)	3/3 (100%)	Peri-lesion	-	Granular (100%)	IgG, IgM, IgA, C3	-
Boddu et al.[64] (2016)	Caucasian (United States)	1/1 (100%)	N/A	-	Granular (100%)	IgG	-
Jain et al.[67] (2016)	Asian (India)	2/2 (100%)	N/A	-	(i) Granular (N/A) (ii) Linear (N/A)	IgG, IgA, IgM, C3	Positive immunoreactants at hair follicle epithelium (N/A)
Hans-Bittner et al.[66] (2017)	Latin America (Brazil)	1/1 (100%)	N/A	-	(i) Granular (N/A) (ii) Linear (N/A)	IgG, IgA, IgM, C3	-
De Risi-Pugliese et al.[62] (2018)	Caucasian (Poland)	135/138 (98%)	N/A	-	(i) Granular (N/A) (ii) Linear (N/A)	IgG (91%) IgA (72%) IgM (68%) C3 (67%)	-
Torres Saavedra et al.[73] (2020)	Latin America (Colombia)	5/5 (100%)	Peri-lesion	-	(i) Linear (75%) (ii) Granular (20%)	IgG (100%) IgM (100%) C3 (80%) IgA (60%)	-

TABLE 1. Literature review of direct immunofluorescence findings in cutaneous lupus erythematosus. (Continued)

Mucosal lupus erythematosusμ							
Study	**Ethnicity**	**Positive DIF (%)**	**Site of skin biopsy**	**DIF findings**			**Others**
				Epidermis	**DEJ**		
					Pattern	**Immunoreactants**	
Daniel et al.[77] (1981)	- (United States)	6/6 (100%)	Lesion	-	Granular (coarse) (100%)	C3 (100%) IgG (50%) IgM (50%) IgA (16.7%)	-
Schiodt et al.[43] (1981)	- (United States)	7/7 (100%)	Lesion	-	(i) Granular (N/A) (ii) Homogenous (N/A)	C3 (100%) IgM (86%) IgG (57%) IgA (43%)	Positive immunoreactants at CB (N/A)
Nikoo et al.[78] (2017)	Persians (Iran)	1/1 (100%)	Lesion	-	N/A	IgG (100%) IgM (100%) C3 (100%)	-
Chanprapaph et al.[14] (2021)	Asian (Thai)	5/6 (83.3%)	Lesion	-	(i) Focal granular (N/A) (ii) Homogenous granular (N/A)	IgG, IgM, IgA, C3	-
Pires et al.[79] (2021)	Latin America (Brazil)	15/15 (100%)	Lesion	-	Granular (100%)	IgG, IgM, fibrinogen	Positive immunoreactants at epidermis and dermis (loose connective tissue at epithelial ridges)
Papulonodular mucinosis							
Study	**Ethnicity**	**Positive DIF (%)**	**Site of skin biopsy**	**DIF findings**			**Others**
				Epidermis	**DEJ**		
					Pattern	**Immunoreactants**	
Rongioletti et al.[82] (1990)	Caucasian (Italy)	2/2 (100%)	Lesion	-	(i) Granular (50%) (ii) Linear (50%)	IgM, C3	-

TABLE 1. Literature review of direct immunofluorescence findings in cutaneous lupus erythematosus. (Continued)

Papulonodular mucinosis							
Study	**Ethnicity**	**Positive DIF (%)**	**Site of skin biopsy**	**DIF findings**			
				Epidermis	**DEJ**		**Others**
					Pattern	**Immunoreactants**	
Kanda et al.[81] (1997)	Asian (Japan)	5/6 (83.3%)	Lesion	-	(i) Linear (60%) (ii) Granular (40%)	IgG (66.7%) IgM (66.7%) IgA (66.7%) C3 (33.3%)	Positive immunoreactants at BV (20%)
		4/6 (66.7%)	Non-lesion	-	(i) Linear (75%) (ii) Granular (75%)	IgG (100%) C3 (66.7%) IgA (66.7%) IgM (33.3%) C1q (33.3%)	-
Dallo et al.[80] (2020)	Caucasian (United States)	1/1 (100%)	Lesion	-	Granular (100%)	IgA, IgM, C3	-
Nonscarring alopecia in systemic lupus erythematosus							
Study	**Ethnicity**	**Positive DIF (%)**	**Site of skin biopsy**	**DIF findings**			
				Epidermis	**DEJ**		**Others**
					Pattern	**Immunoreactants**	
Chanprapaph et al.[27] (2019)	Asian (Thailand)	25/32 (78.1%)	Lesion	ENS (24%)	Homogenous granular (100%)	IgM (76%) C3 (48%) IgG (40%) IgA (16%)	Positive immunoreactants at follicular epithelium (100%) CB (44%), peri-eccrine area (24%) and peri-sebaceous staining (16%)

Abbreviations: BV: blood vessels, C3: complement 3, CB: cytoid bodies, DEJ: dermo-epidermal junction, ENS: epidermal nuclear staining, Ig: immunoglobulin, LE: lupus erythematosus, N/A: not available, TEN: toxic epidermal necrolysis

δ This study demonstrated positive immunoreactants in the nuclear, intracellular cytoplasm and intercellular space of epithelial cells with speckle (DLP) pattern.

ω *Mutasim et al.* demonstrated positive immunoreactants including IgG, IgM, C3 and faint IgA at suprabasal and basal cells with granular pattern.

φ All studies demonstrated epidermal nuclear staining in the epidermis by IgG except *Magro et al.* which revealed C3 with IgG deposition at epidermal nuclear staining.

μ Mucosal lupus erythematosus consisted of oral manifestations of LE, SLE and DLE. The details of each type were not clarified in some articles.

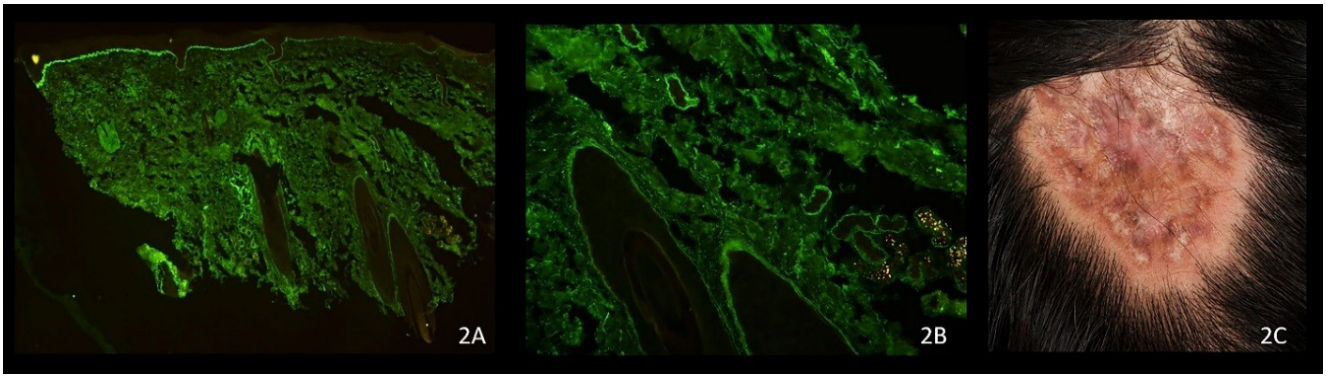

Fig 2A &2B. DIF findings of discoid lupus erythematosus showed deposits of IgM at the DEJ with granular patterns and also extended to the basement membrane of hair follicles or peri-appendage areas. (Figure 2A 4x magnification, 2B 20x magnification).
Fig 2C. Clinical presentation of scalp discoid lupus erythematosus showed well-defined erythematous atrophic plaque with scarring alopecia localized on vertex of scalp.

is less than lichen planus.[43] *Schiødt et al.* analyzed the sensitivity and specificity of DIF in oral DLE lesions and found it to be 92% and 72%, respectively.[43] A skin biopsy of oral DLE is recommended in erythematous areas.[43]

Lupus panniculitis

Lupus panniculitis is another presentation of CCLE characterized by inflammatory processes in subcutaneous fat and the deep dermis. The prevalence of lupus panniculitis is approximately 20%. Lupus panniculitis usually presents itself as erythematous, indurated, painful subcutaneous nodules localized on the face, neck, buttocks, arms and thighs (Fig 3B).[49] The positive yield of DIF tests in lesion skin was 66.7%-100%.[49-51] Although the main pathology of lupus panniculitis is located in the fat lobule, DIF findings are quite similar to other types of cutaneous LE. There were deposits of multiple immunoreactants at the DEJ, followed by positive staining in blood vessels, CB and follicular epithelium[49,50] (Fig 3A). IgM was the most reported immunoreactant in lupus panniculitis.

Lupus erythematosus tumidus

Lupus erythematosus tumidus or tumid LE presents itself as indurated erythematous, or edematous plaques localized prominently in sun-exposed areas such as the head and neck. The clinical course of tumid LE is benign and there is low incidence of systemic involvement.[52] The positive yield of tumid LE in DIF tests was 26.7%-100%.[52-55] The deposits of immunoreactants were mainly at the DEJ[52-55] (Fig 4). ENS or DLP was rarely detected in a DIF test of tumid LE.

Chilblain lupus erythematosus

Chilblain LE, a rare variant of CCLE, presents itself as pruritic purpuric papules or plaques located in areas exposed to the cold such as the ears, fingers and

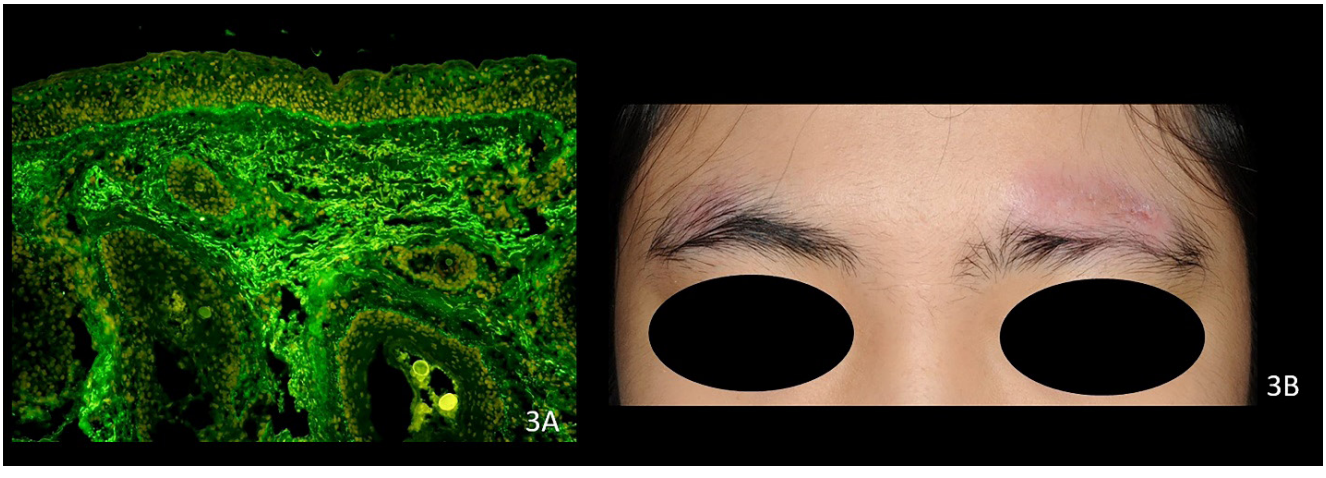

Fig 3A. DIF findings of lupus panniculitis showed granular deposits of IgM at the DEJ, followed by positive staining in follicular epithelium. (20x magnification).
Fig 3B. Clinical presentation of lupus panniculitis showed well-defined erythematous indurated plaque localized at both eyebrows.

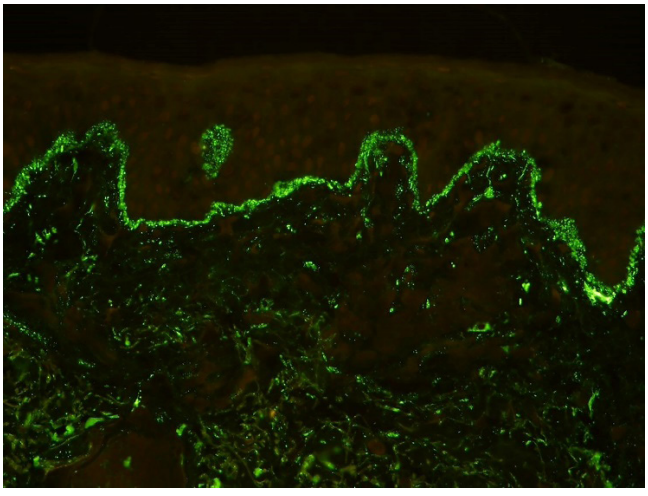

Fig 4. DIF findings of lupus erythematosus tumidus showed granular deposits of IgM at the DEJ with colloid bodies. (20x magnification).

toes. Some lesions of chilblain LE can become a painful ulceration. The prevalence of chilblain LE is around 6% of all LE cases.[56] By clinical presentation, chilblain LE is not decimated from idiopathic chilblains and lupus pernio.

DIF findings of chilblain LE are limited. *Pock et al.* revealed deposits of multiple immunoreactants at the DEJ, and both IgA and IgM staining at the papillary dermis.[56] On other hand, *Patel et al.* discovered only the staining of fibrin at dermal vessels.[57]

Hypertrophic/verrucous lupus erythematosus

Hypertrophic LE, another rare variant of CCLE, is defined by recalcitrant hyperkeratotic scaly plaques in sun-exposed areas. The clinical manifestation imitates other hyperkeratotic cutaneous diseases such as hypertrophic lichen planus and squamous cell carcinoma.

DIF findings of hypertrophic LE are in short supply. *Khorshid et al.* investigated DIF results in one patient with hypertrophic LE and revealed positive multiple immunoreactants at the DEJ in linear pattern and positive ENS by IgG in speckle pattern.[58] Moreover, staining of C3 and fibrinogen in superficial dermal blood vessels was also reported.[58]

Non-specific lupus cutaneous manifestations

Bullous systemic lupus erythematosus

Bullous systemic lupus erythematosus (BSLE) typically presents itself as an acute blister or bullae eruption over normal skin or erythematous lesions in a patient with SLE. These blisters develop commonly in areas exposed to the sun; however, they are also found in areas shielded from the sun or mucosa.[59] BSLE is the result of autoantibodies to type VII collagen which attack non-collagenous domain type 1 and 2 of type VII collagen of the DEJ.[60,61] The correlation between BSLE and systemic involvements including lupus nephritis, neuropsychiatric SLE and hematologic abnormality have been documented.[62]

DIF studies of BSLE are usually performed in the perilesional area with clinical non-lesional skin to demonstrate staining of IgG, IgM, C3 and IgA at the DEJ with linear or granular patterns[35,59,62-74] (Fig 5A & 5B). The positive yield from the DIF test was high, at approximately 85.7%-100%.[35,59,62-74] IgG was the most reported immunoreactant, while IgA was more common in BSLE than other forms of lupus.[65] Furthermore, IgA deposits were associated with disease activity.[65]

DIF findings of BSLE are hard to differentiate from other vesiculobullous diseases such as bullous pemphigoid, epidermolysis bullosa acquisita, and cicatricial pemphigoid. Direct salt-split skin immunofluorescence by 1 mol/L saline is usually performed as an additional step to provide an accurate diagnosis. Deposits of IgG at the dermal side of cleavage blisters in direct salt-split skin

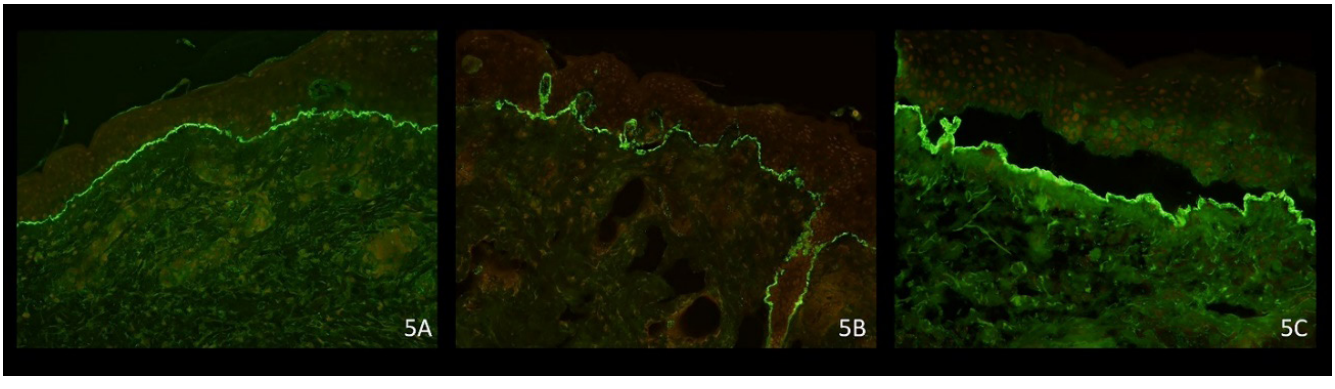

Fig 5A & 5B. DIF findings of bullous systemic lupus erythematosus (BSLE) showed immunoglobulins at the DEJ with linear or granular pattern. (10x magnification).

Fig 5C. Direct salt-split skin immunofluorescence of BSLE showed deposits of immunoglobulin at the dermal side of cleavage blister. (40x magnification)

study support the diagnosis of BSLE and epidermolysis bullosa acquisita. Generally, positive staining at the roof of clevage blisters are found in bullous pemphigoid, and not BSLE (Fig 5C).

Mucosal lupus erythematosus

Mucosal involvement is found in both of cutaneous LE and SLE. Oral mucosa is the most common site (3%-50% of patients with LE) among mucosal areas.[75] The clinical presentations of mucosal LE are generally erythematous macules, which develop into erosions or ulcers. Common locations of oral LE are the lower lip and hard palate.

DIF results of oral LE reveal deposits of multiple immunoreactants at the DEJ with granular pattern[43,77-79] (Fig 6). Moreover, deposits of multiple immunoreactants in loose connective tissue at epithelial ridges, CB and positive fibrinogen in epidermis have also been reported.[43,79] C3 is the most common immunoreactant, followed by IgM, IgG and IgA.[43,77] The positive yield of mucosal areas was around 83.3%-100%.[43,76-79] The advantage of an DIF test in this scenario is that it helps differentiate e oral LE from other oral lichenoid lesions.

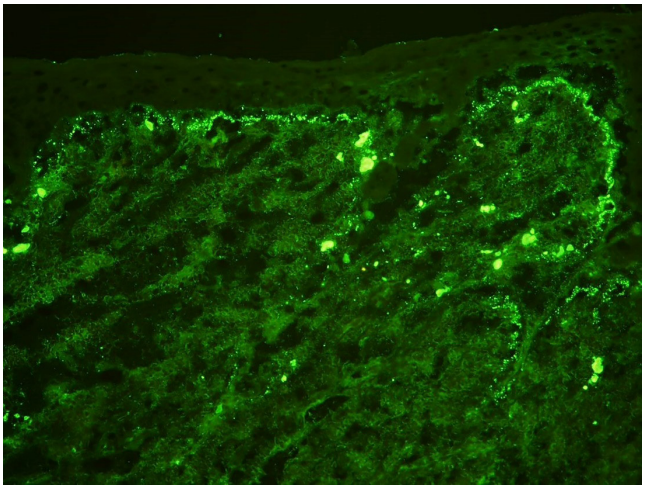

Fig 6. DIF findings of mucosal lupus erythematosus showed granular deposits of complement 3 at the DEJ with colloid bodies. (10x magnification).

Papulonodular mucinosis

Papulonodular mucinosis is a nonspecific variant of cutaneous LE which reveals mucin deposition in the dermis with minimal or no interface change by histopathology. It usually manifests as asymptomatic skin-colored papulonodular lesions on the trunks or extremities. Papulonodular mucinosis is categorized as primary cutaneous mucinosis. It cannot be distinguished from other cutaneous mucinoses such as lichen myxedematosus, scleredema and cutaneous focal mucinosis through histopathology.

The positive yield in DIF studies ranges from 83.3%-100% in areas with lesions and is 66.7% in non-lesion areas[80-82] (Table 2). Multiple immunoreactants are predominantly demonstrated at the DEJ with linear or granular patterns[80-82] (Table 1). LB is also observed in papulonodular mucinosis and staining in blood vessels has also been reported.[81] Moreover, *Kanda et al.* investigated uninvolved skin and displayed discontinuous and weak staining bands at the DEJ which was insufficient for designation as a positive LB.[81] However, the DIF findings of papulonodular mucinosis is not different from other types of CCLE.

Nonscarring alopecia in systemic lupus erythematosus

Nonscarring alopecia is also a common manifestation of nonspecific LE lesions and ranges from 17%-80%.[27] Its histopathology exhibits interface dermatitis along the DEJ or follicular epithelium according to LE specific changes. The correlation between nonscarring alopecia and disease activity of systemic involvement is known. When progressive diffuse hair loss is detected, there is an increase in reports of major organ involvement.[74]

DIF findings of nonscarring alopecia mostly revealed deposits of multiple immunoreactants at the DEJ with homogeneous granular patterns and follicular epithelium.[27] Additionally, ENS, CB and deposits in peri-eccrine and peri-sebaceous areas were also reported.[27] The positive yield in the DIF test was approximately 78.1%, with IgM being the most common immunoreactant.[27] DIF findings of several clinical manifestations of nonscarring alopecia in SLE, including mild diffuse alopecia, severe diffuse alopecia, patchy alopecia, and lupus hair are not different.[27]

DISCUSSION

Typically, DIF tests of cutaneous LE reveal deposits of multiple immunoreactants at the DEJ with linear or granular patterns, known as LB which is more common in SLE (70%) than mixed connective tissue diseases (13.5%-33%) and scleroderma (33%).[23,83] IgM is the most common immunoreactant while the least is IgA. The exact mechanism of immunoglobulin deposition at DEJ in the LE patients still needs to be elucidated. It is believed that immunoreactants are not antibodies against DEJ components but rather represent circulating immune complexes of deoxyribonucleic acid (DNA) and ANA trapped within the DEJ.[11] Furthermore, DNA released from ultraviolet-injured keratinocytes, although diffusing across the DEJ, may bind to collagen IV and serve as an antigen for circulating autoantibodies.[11] It should be noted that, sometimes, sun-damaged skin can show

TABLE 2. Characteristics of direct immunofluorescence studies in cutaneous lupus erythematosus.

Characters	SLE	Specific LE lesions								Non-specific LE lesions		
		ACLE	SCLE	DLE	Lupus panniculitis	CCLE LET	Chilblain LE	Hypertrophic LE	BSLE	Mucosal LE	Papulonodular alopecia	Nonscarring mucinosis
Positive yield	42-100% (Lesional) 32-92.2% (Non-lesional)	60-100% (Lesional) 25% (Non-lesional)	34-100% (Lesional) 36-100% (Non-lesional)	27.2-100% (Lesional) 45.5-69.2% (Non-lesional)	66.7-100% (Lesional)	26.7-100% (Lesional)	100%* (Lesional)	100%* (Lesional)	85.7-100% (Peri-lesional)	83.3-100% (Lesional)	83.3-100% (Lesional) 66.7% (Non-lesional)	78.1% (Lesional)
Sensitivity	81.8%	60%	20-45%	55-92% (Cutaneous and oral)	-	-	-	-	-	-	-	-
Specificity	95.6%	-	-	72% (Oral)	-	-	-	-	-	-	-	-
Common immunoreactants	IgM	-	IgG, IgM	-	IgM	-	-	-	IgG	C3	-	IgM

Abbreviations: ACLE: acute cutaneous lupus erythematosus, C: complement, CCLE: chronic cutaneous lupus erythematosus, CLM: cutaneous lupus mucinosis, DLE: discoid lupus erythematosus, Ig: immunoglobulin, LE: lupus erythematosus, LET: lupus erythematosus tumidus, SCLE: subacute cutaneous lupus erythematosus, SLE: systemic lupus erythematosus

* Chilblain LE and hypertrophic LE were reported as case report.

positive DIF results which are similar to cutaneous LE. The positive LB group has a reported higher incidence of systemic involvements and autoantibodies, and a poorer prognosis than the negative group.[11] Furthermore, its sensitivity for predicting active disease is higher than other laboratory parameters, including serum C3 and C4 levels, erythrocyte sedimentation rate, lymphocyte count, and anti-double stranded DNA antibodies.[21,24]

Table 2 summarizes positive yields of DIF studies among cutaneous LE subtypes. The sensitivity of non-lesion areas is reported to be lower than lesion areas.[8] Thus, to obtain higher positive yields, a skin biopsy should be performed at active lesions that are over a month old.[10,12] DIF findings among cutaneous LE subtypes also overlap. Thus, diagnosis of cutaneous LE requires a combination of monitoring patient history, physical examinations, and laboratory studies. Antibodies serology and DIF studies help confirm diagnosis and at times determine disease severity.

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