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Review

Pathogenesis of cutaneous lupus erythema associated with and without systemic lupus erythema

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ABSTRACT

Cutaneous lupus erythematosus (CLE) can be an individual disease only involving skin, or presents as part of the manifestations of SLE. A small proportion of CLE may progress into SLE, however, the underlying pathogenic mediators remain elusive. By only including researches that clearly described if the subtypes of CLE presented by enrolled subjects was associated with or without SLE, we provided an overview of antibodies, inflammatory cells and inflammatory molecular mediators identified in blood and skin that were possibly involved in lupus skin damages. IgG autoantibodies are crucial for the development of CLE associated with SLE, but the circulating inflammatory cells and molecular mediators require further studies to provide definitive proof for their association with skin damages. Discoid lupus erythematosus (DLE) is the most common subtype of CLE. For DLE without associated with SLE (CDLE), it is lack of evidences if autoantibodies and circulating inflammatory cells are involved in the pathogenesis or not, but is clear that the cutaneous inflammatory infiltrates are dominated by Th1, but not Th17 cells in contrast to the various complex profile in SLE. As the major target cells in skin, keratinocytes may participate the pathophysiological process by increase cell apoptosis and the production of proinflammatory cytokines in SLE and CDLE. Insights into the similarities and differences of the pathogenesis of CLE and CLE associated with SLE will also improve our therapeutic strategies for CLE that is currently adopted from SLE, and prevent the progression of CLE to SLE by providing interventions within an appropriate window of disease development.

Contents

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1. Introduction

Cutaneous lupus erythematosus (CLE) is an autoimmune disease including a wide range of dermatologic manifestations. According to the clinical and histological appearances, duration of symptoms and associated laboratory disorders, CLE is divided into acute (ACLE), subacute (SCLE), and chronic (CCLE) varieties. Discoid lupus erythematosus (DLE) belongs to the category of CCLE, is the most common specific skin manifestations of lupus and represents up to 80% of all cutaneous lupus cases [1]. CLE cases, can only have skin damages without extracutaneous involvement, or progress into systemic lupus erythematosus (SLE) with at least one internal organ involvement and immune serological disorders, or occur at any stage of SLE disease. The progression from CLE to SLE occurs in approximately 20% of patients [1,2], and about 70% of patients with SLE develop cutaneous lesions at some point in their lives [3]. Clearly, there are crosslinks between CLE and systemic involvements of SLE, however, on the other hand, a proportion of CLE cases never develop SLE and some SLE patients never present CLE manifestations, suggesting that the two entities may share some similarities, and preserve some differences in the pathogenesis of skin damage [4].

As for SLE, skin is the second most commonly affected organ and the second most frequent site (20%) of initial clinical presentation [5,6]. Moreover, mucocutaneous related manifestations including malar rash, discoid rash, photosensitivity, and oral ulcers are 4 of 11 diagnostic criteria presented by the American College of Rheumatology [5,6]. Thus, skin involvement not only contributes to, but facilitates the early diagnosis of SLE. Moreover, SLE patients with ACLE may have more severe systemic disease over time [7], whereas SLE patients with DLE are less likely to develop end-stage organ damages, but tend to have lower prevalence of renal involvement and disease activity, suggesting that the subtypes of CLE could be a marker predicting disease activity and prognosis of SLE [8–14]. Therefore, the potential diagnostic and prognostic values of lupus skin damages make it imperative to understand the pathophysiologic pathways involved in CLE with and without systemic abnormalities.

These facts, together with the relative visibility and accessibility of cutaneous lesions compared to lesions in the other organs, highlight skin as a key organ to study end-organ pathology in SLE and to extend our understanding of CLE as part of the systemic autoimmune disorders or as an independent entity. Thus, this review only included researches that clearly clarified if the enrolled CLE patients with or without SLE. The pathogenesis of CLE regardless of its association with SLE was beyond the scope of this review, and instead, has been generously and well reviewed elsewhere recently [15–24]. Moreover, for convenience sake, we described SLE patients with subtypes CLE as: SLE + ACLE+, SLE + SCLE+, SLE + DLE+ and SLE + CLE+ in this review. We summarized recent findings on progression of CLE to SLE, and discussed the pathogenesis of lupus skin damage in SLE patients with CLE, and in CDLE patients with skin as the sole involved organ and without any systemic disorders. We provided an overview of antibodies, inflammatory cells and inflammatory mediators identified in blood and skin that were possibly involved in lupus skin damages (Tables 1 & 2), explored the role of keratinocytes in the pathophysiological process, and outlined the genetic and epigenetic susceptibility to SLE + CLE+ and CDLE.

2. Progression of CLE to SLE

A small percentage of patients with CLE eventually develop SLE. In a prospective, longitudinal cohort study of 77 patients with CLE, 13 (17%) went on to meet criteria for SLE within an average time of 8.03 ± 6.20 years (mean ± SD) [2]. In line with this study, a research group from Sweden showed that about 107 (18%) patients with CLE developed SLE during the observation period (2005–2007) [1]. For pediatric patients, in a retrospective study of 34 subjects with DLE, 9 eventually met SLE criteria, 15 developed laboratory abnormalities without meeting SLE criteria, and 10 maintained skin-limited disease. The average age at progression to SLE was 11 years, with greatest risk in the first year after DLE diagnosis [8]. Generally, patients with SCLE displayed a higher probability to develop SLE, whereas those with CDLE, especially localized DLE predicted toward a skin limited form of the disease [1,13].The clinical and laboratory risk factors of SLE development in patients with DLE include widespread DLE lesions, arthralgia/arthritis, nail changes, anemia, leucopenia, high erythrocyte sedimentation rates (ESRs) and high titers of antinuclear antibodies (ANAs) [41]. Most of CLE patients received the diagnosis of SLE by meeting the mucocutaneous ACR criteria and carried none to mild phenotype of SLE without developing end-organ damage as long as over 5 years of median follow-up [2,8]. Moreover, the subsets of CLE associated with SLE could be a mark predicting SLE disease activity. As for DLE lesions, two studies were performed to investigate the association of DLE with each ACR criteria, one with 1043 SLE patients (117 with DLE and 926

Table 1
Serum inflammatory mediators associated with lupus skin damage.

	SLE^+							SCLE v.s	CDLE v.s		
	v.s HC	$skin^-$ v.s HC	$skin^+$ v.s HC	$skin^+$ v.s $skin^-$	DLE^+ v.s HC	$SCLE^+$ v.s HC	DLE^+ v.s SCLE+	HC	HC	SLE	SLE^+ DLE^+
Th1, Th17, Th22 [25]			>[25]				>[25]				
Th2 [25]			>[25]				=[25]				
pDCregs [25]			>[25]								
Tregs [25]					=[25]	=[25]					
Bregs [25]					>[25]	=[25]					
IL-17(A/F) [25–27]	>[27]	>[26]$^{(A,F)}$		>[27]	>[25]	>[25]	>[25]	>[26]$^{(A,F)}$	>[26]$^{(A,F)}$		
IL-23[26,27]	>[27]	=[26]						=	=		
IL-6[28,29]	>										
IL-22[25]					=[25]	<[25]					
sCXCL16 [30]	>			>							
IL-10[25,31]	=[31]		=[25]				>[25]		<[31]	<[31]	
TGF-β [31]	=[31]								<[31]	=[31]	
BAFF, BAFF-R [32]					>				=		=

Symbols: >: significantly higher; <: significantly lower; =: no difference; HC, healthy control.