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Review article

THE IMPACT OF HOMOCYSTEINE IN LUPUS ERYTHEMATOSUS: A LINK OF INFLAMMATION, SKIN AND CARDIOVASCULAR RISK

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Abstract

Lupus erythematosus (LE) is a complex autoimmune disease with diverse clinical manifestations, ranging from systemic involvement to cutaneous lesions. Cutaneous lupus erythematosus (CLE) is the second most common manifestation of LE, resulting in disfiguring scaring, hair loss and significant burden for the patients' quality of life.

Elevated homocysteine (Hcy) levels, or hyperhomocysteinemia (HHcy), are observed in both SLE and CLE. Hcy contributes to endothelial dysfunction, thrombosis risk, and immune activation through pro-inflammatory cytokine release, oxidative stress, and vascular damage. Additionally, it disrupts T-cell function and epigenetic regulation, further exacerbating autoimmune responses.

Several factors can cause HHcy, including genetics (such as MTHFR mutations), kidney problems, metabolic disorders, certain medications, and deficiencies in B vitamins (B6, B9, B12). Since B vitamins help regulate Hcy, a poor diet or an inability to properly absorb nutrients may contribute to higher Hcy levels in lupus patients. Additionally, HHcy is a recognized risk factor for cardiovascular disease (CVD), a major cause of morbidity in lupus patients. Increased Hcy levels contribute to arterial stiffness, endothelial injury, and thrombotic complications, elevating the risk of atherosclerosis, stroke, and myocardial infarction.

Hcy may act as a biomarker for disease severity and vascular risk in CLE. Interventions such as B-vitamin supplementation and lifestyle changes could offer therapeutic benefits. However, further research is needed to clarify its role in CLE pathogenesis and its potential for clinical management.

Keywords: homocysteine, lupus erythematosus, inflammation, cardiovascular risk

Introduction

Cutaneous lupus erythematosus (CLE) is an autoimmune disease that can present either as an isolated skin disease or as a manifestation within the spectrum of systemic lupus erythematosus (SLE). CLE is the second most common manifestation of SLE, resulting in disfiguring scars, hair loss, and a significant burden on the patients' quality of life. CLE is a complex autoimmune disease with multifactorial etiology, including epigenetic, genetic, environmental, and external factors. The disease occurs in all ethnic and age groups. Over 90% of cases are women of reproductive age [1].

Cutaneous lupus erythematosus (CLE) is relatively common, with an incidence rate close to that of systemic lupus erythematosus (SLE), reaching 4.3 cases per 100,000 people. Its chronic subtypes have an even higher prevalence, reported in some studies at 70 cases per

100,000 people [2,3]. Like SLE, CLE predominantly affects women, with a female-to-male ratio of 4:1, and occurs more frequently in African-Americans compared to Caucasians [2].

Contemporary classifications of lupus erythematosus

Lupus erythematosus (LE) encompasses a broad spectrum of clinical manifestations, ranging from mild cutaneous involvement to severe, life-threatening systemic complications. Cutaneous lupus erythematosus (CLE) is a prevalent subset, affecting up to 85% of LE patients and, in some cases, representing the sole clinical manifestation [3]. CLE classification is based on clinical presentation, histopathological features, symptom duration, and associated immunological markers, offering critical diagnostic and prognostic insights [4].

Gilliam and Sontheimer divided CLE based on the clinical picture into three types: acute CLE (ACLE), subacute CLE (SCLE), and chronic CLE (CCLE), which constitute the specific lesions (Table 1). Acute cutaneous lupus erythematosus (ACLE) is a common manifestation of systemic lupus erythematosus (SLE), as nearly half of SLE patients present with this subtype of cutaneous lupus erythematosus (CLE). Almost all patients with ACLE (80–90%) have SLE. ACLE typically appears as a localized facial eruption; often, it presents as a sun-induced malar or butterfly rash. Less commonly, it manifests as a generalized, symmetrically distributed eruption [5]. The most common manifestation of chronic CCLE is discoid lupus (DLE), which presents as indurated erythematous plaques and papules that can result in significant scarring and alopecia. SCLE patients are particularly photosensitive and present with erythematous papulosquamous or annular-polycyclic plaques that tend to heal with residual post-inflammatory dyspigmentation [6].

Subacute cutaneous lupus erythematosus (SCLE) commonly affects sun-exposed areas and presents in two primary forms: annular and papulosquamous rashes. It may also be associated with systemic symptoms, including arthritis and myalgias. Approximately 50% of patients with SCLE fulfill the diagnostic criteria for systemic lupus erythematosus (SLE), as established by the American College of Rheumatology and the Systemic Lupus International Collaborating Clinics [7].

A large multicenter database analysis from the European Society of Cutaneous Lupus Erythematosus revealed that 72.1% of SCLE patients tested positive for anti-Ro/SSA antibodies. This high prevalence may explain why SCLE is more frequently associated with Sjögren's syndrome (SS) compared to chronic cutaneous lupus erythematosus (CCLE). Anti-Ro/SSA antibodies are commonly found in various autoimmune conditions, including SLE, SS, SCLE, and SS/SLE overlap syndromes [8].

CCLE comprises several subtypes, with discoid lupus erythematosus (DLE) being the most prevalent and recognizable, accounting for approximately 80% of CCLE cases. Other less common subtypes include verrucous lupus erythematosus (VLE), lupus erythematosus profundus (LEP), chilblain lupus erythematosus (CHLE), and tumid lupus erythematosus (LET) [6].

There are also a number of skin lesions that are relatively common in lupus patients but are not specific to lupus, including livedo reticularis, vasculitis, Raynaud's phenomenon, and alopecia areata. Non-specific lesions, such as Raynaud's phenomenon, periungual teleangiectasias, livedo reticularis or leukocytoclastic vasculitis, are also frequently associated with SLE. Diagnosing CLE requires proper classification of skin lesions into one of the three subtypes mentioned above [6].

Table 1. Gilliam's classification (1981)[5]

LE-specific lesions	LE-nonspecific lesions
• Acute cutaneous lupus erythematosus (ACLE) • Localized form • Generalized form • Subacute cutaneous lupus erythematosus (SCLE) • Annular form • Papulosquamous form • Chronic cutaneous lupus erythematosus (CCLE) • Discoid lupus erythematosus (DLE) • Localized form • Disseminated form • Lupus erythematosus profundus • Chilblain lupus erythematosus (CHLE) • Intermittent cutaneous lupus erythematosus (ICLE) • Lupus erythematosus tumidus (LET)	• Leukocytoclastic vasculitis • Palpable purpura • Urticarial vasculitis • Livedo racemosa • Thrombophlebitis • Occlusive vasculopathy • Raynaud's syndrome • Periungual telangiectases • Diffuse nonscarring alopecia • ("lupus hair") • Calcinosis cutis • Papular mucinosis • Erythema multiforme

Diagnostic Considerations and Pathophysiological Implications

CLE diagnosis necessitates a comprehensive assessment integrating clinical morphology, histopathological examination (characterized by vacuolar interface dermatitis and perivascular/periadnexal lymphocytic infiltrates), and serological profiling [9]. Direct immunofluorescence (DIF), while useful in specific contexts, is not a definitive diagnostic criterion[10]. Emerging evidence underscores potential systemic ramifications of CLE, including chronic inflammation and heightened cardiovascular risk [11]. Notably, hyperhomocysteinemia, a recognized mediator of endothelial dysfunction and thrombogenesis, has been implicated in autoimmune pathophysiology, warranting further investigation into its role in CLE-associated cardiovascular morbidity [12,13]. Future research should elucidate the interplay between CLE, dysregulated homocysteine metabolism, and systemic inflammatory pathways to refine therapeutic strategies and risk stratification protocols.

This review aims to bridge these interconnected domains of cutaneous autoimmunity, systemic inflammation, and vascular risk by examining the potential cross-talk between CLE, homocysteine metabolism, and cardiovascular comorbidities. By doing so, we hope to shed light on under-investigated mechanisms that contribute to broader clinical picture of CLE and identify future research and management directions.

CLE and Systemic Inflammation

Cutaneous lupus erythematosus (CLE) is a complex, multifactorial condition that has been extensively studied. Across its various subtypes, a dynamic interplay between the innate and adaptive immune systems sustains a self-perpetuating inflammatory cycle [14]. This process is initiated by keratinocyte destruction, often triggered by external factors such as ultraviolet (UV) radiation and certain medications [15]. Additionally, research suggests that smoking increases the risk of CLE [16].

When keratinocytes are damaged, cellular debris is released into the extracellular space, activating danger-sensing receptors, triggering an inflammatory cascade, recruiting immune cells, and intensifying the response [14]. A central driver of CLE progression is the excessive activation of interferons (IFNs), which induce an inflammatory state resembling an antiviral defense mechanism [17]. Type I interferons (IFNs) are a class of immunomodulatory cytokines that play a crucial role in the innate and adaptive immune systems. They serve as a defense mechanism against viral infections and contribute to cancer immunosurveillance. Increasing evidence suggests that type I IFNs are also key drivers in the initiation and persistence of autoimmune and inflammatory skin diseases, including CLE [18].

Type I IFNs are produced by various cell types, including leukocytes, fibroblasts, endothelial cells, and keratinocytes [19]. However, their dominant source and function can vary based on disease context. The cytokine profile and inflammatory cell composition in CLE are highly heterogeneous, influencing disease progression. IFNs present a group of 17 immune signaling proteins, including several types of IFN-α and others like IFN-β and IFN-κ. They all work through the same receptor, IFNAR, which is found in nearly all cells. When activated, IFNAR triggers a signaling pathway (JAK-STAT) that leads to the creation of a protein complex called ISGF3, which enters the cell nucleus and turns on genes that help fight viruses and regulate the immune system [20]. Because of their powerful role in immune responses, especially in inflammation, type I IFNs are being targeted in new treatments for autoimmune skin diseases like CLE [21].

There is substantial evidence that type I IFNs are important in propagating ongoing disease activity in SLE [22]. Previous studies have demonstrated that elevated type I IFN in blood is associated with increased disease activity in cross-sectional studies. Despite this robust association, longitudinal studies generally do not support the idea that IFN levels fluctuate predictably with changes in SLE disease activity [23]. These findings suggest that type I IFN levels demarcate groups of patients that are more or less likely, on average, to have higher disease activity and flares at any given time. However, type I IFN may not be highly informative as a longitudinal biomarker, which is supported by a recent study in which elevations of type I IFN in patients in remission were associated with a higher risk of relapse[24]. Recent findings highlight the central role of circulating cytokines in the pathogenesis of cutaneous lupus erythematosus (CLE). Elevated levels of type I interferons (particularly IFN-α) and IL-17A were observed across CLE subtypes and correlated with skin disease activity, as measured by the CLASI score. IFN-α was more strongly expressed in skin lesions than blood, reinforcing its relevance to local cutaneous inflammation. IFN-κ1, although elevated in CLE patients with skin involvement, especially in DLE and SCLE, showed inconsistent correlation with disease activity. However, it remains a key mediator as evidenced by its expression in keratinocytes and findings from murine models [25].

Similarly, IL-17 family cytokines, particularly IL-17A and IL-17F, were associated with CLE activity. IL-17A correlated with disease severity across all subtypes, while IL-17F was linked specifically to DLE. These cytokines contribute to subtype-specific immune responses and represent potential therapeutic targets, as demonstrated by emerging clinical trials targeting the IL-17 pathway. Collectively, these data support a model in which CLE is driven by a network of circulating cytokines with subtype-dependent expression profiles, offering insight into personalized treatment strategies [26].

In a cohort of systemic lupus erythematosus patients without clinical cardiovascular disease (CVD), type I interferon (IFN) activity was independently associated with subclinical vascular damage, including impaired endothelial function, increased carotid intima-media thickness (CIMT), and greater coronary artery calcification. These associations remained significant after adjusting for traditional CVD risk factors, suggesting that immune-driven

mechanisms - particularly type I IFN signaling - play a central role in lupus-associated vascular pathology. Notably, no equivalent studies have yet explored this association in cutaneous lupus erythematosus (CLE), leaving a critical gap in our understanding of cardiovascular risk in CLE populations [27].

Although systemic lupus erythematosus research has explored the role of type I IFNs in promoting atherosclerosis and endothelial dysfunction, the connection in CLE has not been as widely studied. Therefore, there is a gap in research regarding the direct association between type I IFNs and CVD risk in CLE patients.

Elevated homocysteine (HCY) levels have been linked to immune and inflammatory dysregulation, even in otherwise healthy individuals. In a large population-based study, HCY levels showed significant associations with inflammatory markers, including an inverse correlation with complement C4 and positive associations with C-reactive protein (CRP) and immunoglobulin M (IgM). These findings support the role of hyperhomocysteinemia as an immunomodulatory factor, potentially contributing to chronic inflammatory conditions [28].

In parallel, the pro-inflammatory cytokine interleukin-17A (IL-17A) has contributed to immune dysregulation in CLE, with elevated levels observed across disease subtypes. Recent studies suggest a synergistic role between homocysteine and IL-17A in promoting inflammatory pathways, highlighting a possible link between metabolic and immune-mediated mechanisms[29]. This convergence may be particularly relevant in CLE, where systemic inflammation is increasingly suspected, yet remains poorly characterized outside the context of systemic lupus erythematosus [30].

Elevated serum homocysteine (Hcy) and interleukin-17A (IL-17A) levels have been associated with increased disease severity and immune dysregulation. In a recent study examining patients with autism spectrum disorder (ASD), both Hcy and IL-17A levels were significantly higher in affected individuals compared to healthy controls. These elevations were most pronounced in those with severe ASD, who also exhibited reduced folate and vitamin B12 levels. Importantly, Hcy and IL-17A levels positively correlated with disease severity, suggesting a potential pathogenic role for hyperhomocysteinemia and IL–17–driven inflammation. These findings may have broader implications for immune-mediated conditions, including cutaneous autoimmune diseases such as CLE, where similar inflammatory pathways may be at play [29].

Emerging research has highlighted the involvement of IL-17 family cytokines, particularly IL-17A and IL-17F, in the inflammatory landscape of cutaneous lupus erythematosus (CLE). Tanasescu *et al.* demonstrated elevated IL-17A expression in skin lesions and serum of patients with discoid lupus erythematosus (DLE), a common CLE subtype, suggesting a strong correlation between IL-17A levels and disease severity. Additionally, IL-17F concentrations were found to be higher in DLE, subacute cutaneous lupus erythematosus (SCLE), and systemic lupus erythematosus patients compared to healthy controls, indicating a broader role of IL-17F in lupus pathogenesis [31].

Furthermore, elevated homocysteine levels have been associated with increased IL-17A expression in autoimmune conditions. Research indicates that hyperhomocysteinemia can upregulate IL-17A expression via specific molecular pathways, contributing to the progression of various autoimmune diseases. This suggests a potential immunometabolic axis where homocysteine may not only serve as a marker of vascular risk but also actively contribute to the cytokine milieu that perpetuates skin and systemic inflammation in CLE patients [32].

These findings underscore the complex interplay between metabolic factors and cytokine networks in CLE, highlighting the need for further research into targeted therapies that address both the inflammatory and metabolic components of the disease.

Homocysteine in Inflammation and Disease Pathophysiology

Homocysteine (Hcy), a sulfur-containing amino acid derived from methionine metabolism, is widely recognized as a pro-inflammatory mediator implicated in various pathological conditions, including cardiovascular disease (CVD), autoimmune disorders, and chronic inflammatory states [33]. While hyperhomocysteinemia (HHcy) is established as an independent risk factor for vascular dysfunction, its exact role - whether causal or consequential - remains under investigation [34].

Homocysteine, Inflammatory Pathways, and Immune Activation

Evidence suggests that Hcy acts as a pro-inflammatory agent by inducing oxidative stress and endothelial dysfunction [35]. It promotes the generation of reactive oxygen species (ROS), leading to lipid peroxidation, protein damage, and DNA instability, collectively exacerbating vascular inflammation [36]. Moreover, Hcy reduces nitric oxide bioavailability, impairing endothelial function and promoting atherosclerotic plaque formation. Elevated Hcy levels are associated with increased expression of pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, IL-12, and IL-18, as well as acute-phase proteins such as CRP [37]. These cytokines contribute to vascular remodeling, leukocyte adhesion, and smooth muscle cell proliferation, facilitating the progression of atherosclerosis and thrombosis. Additionally, Hcy influences extracellular matrix remodeling by stimulating the overproduction of collagen, elastin degradation, and increased metalloproteinase activity, leading to arterial stiffening and hypertension [38].

Beyond vascular inflammation, Hcy has also been implicated in autoimmune diseases. It can modify proteins through structural alterations, leading to the formation of neoantigens that trigger aberrant immune responses. This mechanism is particularly relevant in conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD), where chronic immune activation is a hallmark feature [39]. Elevated Hcy levels in autoimmune patients correlate with increased IL-18 concentrations, further supporting its role in Th1-mediated immune responses [40]. Additionally, Hcy can modulate the activity of T and B lymphocytes, enhancing cytokine secretion and perpetuating the inflammatory cycle[41]. A 2004 study demonstrated that Hcy and its intermediates can directly activate T lymphocytes, increasing pro-inflammatory cytokine secretion and immune dysregulation. Hcy also induces the upregulation of adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), enhancing monocyte recruitment and exacerbating endothelial dysfunction [42].

Clinical and Immunological Implications of Hyperhomocysteinemia

Recent studies underscore a bidirectional relationship between Hcy and inflammation, wherein inflammatory processes exacerbate HHcy, and elevated Hcy levels further stimulate immune activation [43]. This interconnection is particularly evident in chronic renal disease, where impaired clearance leads to systemic inflammation and vascular dysfunction [44]. Elevated serum creatinine, an indicator of renal impairment, positively correlates with fasting Hcy levels, reinforcing the significance of renal function in homocysteine metabolism [45]. Furthermore, Hcy influences complement system components, particularly complement C4, which has been inversely correlated with Hcy concentrations, suggesting an immune-regulatory role [46]. The interaction between Hcy and inflammatory mediators extends to metabolic diseases, including diabetes, where Hcy exacerbates insulin resistance by promoting oxidative stress and endothelial dysfunction. In type 2 diabetes, elevated IL-18 levels have been linked to increased Hcy concentrations, suggesting a mechanistic overlap between metabolic inflammation and HHcy-driven vascular complications [47].

Emerging evidence also suggests that Hcy contributes to neuroinflammation, which may play a role in neurodegenerative diseases such as Alzheimer's disease (48). Elevated Hcy levels have been associated with blood-brain barrier dysfunction, increased pro-inflammatory cytokine production within the central nervous system, and neuronal damage mediated by oxidative stress (49). These findings further highlight the broad systemic impact of HHcy in vascular and autoimmune disorders, positioning it as a central player in chronic inflammatory diseases. Future research should focus on elucidating the precise molecular mechanisms linking HHcy to immune dysregulation, with potential implications for targeted therapeutic interventions.

Cardiovascular Disease in CLE Patients

Chronic inflammatory diseases, such as cutaneous lupus erythematosus (CLE), impose a significant medical burden [50]. In several chronic autoimmune diseases - including psoriasis, inflammatory bowel diseases, and rheumatoid arthritis - cardiovascular risks are well-documented, and their pathophysiological mechanisms have been extensively studied [51,52]. However, there is limited evidence regarding a potential etiologic link between thromboembolism and CLE.

Chronic inflammation, a hallmark of autoimmune diseases, can contribute to endothelial dysfunction, atherosclerosis, and an elevated risk of cardiovascular events such as myocardial infarction and stroke [53]. Additionally, some patients with CLE may develop metabolic syndrome, characterized by hypertension, dyslipidemia, insulin resistance, and obesity [54]. These comorbidities are likely influenced by the inflammatory nature of CLE and the side effects of long-term treatments, such as corticosteroids [55].

Cardiovascular disease (CVD) has emerged as a significant comorbidity in patients with autoimmune diseases due to shared inflammatory and immune-mediated pathways [56].

CVD remains a leading cause of morbidity and mortality worldwide [57].

In autoimmune diseases like lupus, including cutaneous lupus erythematosus, CVD risk is disproportionately high due to chronic inflammation, immune dysregulation, and specific autoantibodies. While the connection between systemic lupus erythematosus and CVD is well-established, evidence suggests that CLE, even in isolation, contributes to an elevated cardiovascular risk [58].

A study published in *Lupus Science & Medicine* examined 370 patients with CLE, both with and without systemic lupus erythematosus. The findings revealed that individuals with CLE are often undertreated concerning cardiovascular risk factors, leading to a higher incidence of atherosclerotic cardiovascular disease (ASCVD) events, such as heart attacks and strokes [59].

A study by Olbrich *et al*. (2023) examined the relationship between cutaneous lupus erythematosus (CLE) and the risk of cardiac and vascular diseases using a large-scale, propensity-matched retrospective cohort approach. The researchers found that individuals with CLE had a significantly increased risk of developing cardiovascular and vascular conditions compared to matched controls without CLE. Several cardiovascular diseases were found in higher frequencies after diagnosis of DLE and, to a lesser extent, in patients with SCLE, especially thromboembolic events [60].

The Danish nationwide cohort study by Ahlehoff *et al.* investigated the risk of venous thromboembolism (VTE) in patients with cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) compared to the general population. The study included 3,234 patients with CLE, 3,627 with SLE, and 5,590,070 individuals from the reference population. The incidence rates of VTE per 1,000 person-years were 3.06 for CLE patients, 5.24 for SLE patients, and 1.20 for the reference population. After adjusting for potential confounders, CLE

was associated with a hazard ratio (HR) of 1.39 (95% confidence interval [CI] 1.10–1.78) for VTE, while SLE had an HR of 3.32 (95% CI 2.73–4.03), both compared to the reference group. These findings indicate that both CLE and SLE are significant risk factors for VTE, underscoring the need for heightened awareness and further research into thromboembolic complications in patients [61].

While cardiovascular risks in other chronic inflammatory diseases are well-established, the link between CLE and thromboembolism remains underexplored. The pro-inflammatory cytokines and pathways in CLE pathogenesis suggest a potential connection to cardiovascular disease. Further research is needed to elucidate these mechanisms and evaluate the role of treatments like antimalarials in reducing cardiovascular risk in CLE patients [60].

Patients with CLE, especially those with systemic involvement, may already have an increased risk of cardiovascular disease (CVD) due to chronic inflammation. Elevated homocysteine is a known risk factor for vascular damage and thrombosis, which could further worsen cardiovascular outcomes in CLE patients. Investigating this relationship may help identify additional risk factors for heart disease in CLE individuals.

Conclusion

Exploring and understanding the role of homocysteine in cutaneous lupus erythematosus could highlight broader connections between autoimmune diseases and metabolic disturbances, providing a more comprehensive approach to CLE management by considering both immune dysfunction and metabolic health. Emerging evidence suggests that homocysteine plays a critical role at the intersection of inflammation and cardiovascular pathology, extending its relevance beyond traditional metabolic and vascular disorders. In CLE, a condition characterized by chronic immune dysregulation, elevated homocysteine levels may contribute to a pro-inflammatory state through oxidative stress, endothelial dysfunction, and cytokine induction - including IL-1β, IL-6, and IL-17A - mediators known to be elevated in CLE and implicated in atherosclerotic processes. While hyperhomocysteinemia is well-established as a risk factor for cardiovascular disease in the general population and in systemic lupus erythematosus, its specific contribution to cardiovascular risk in CLE remains poorly understood. Given the shared inflammatory pathways and preliminary correlations observed in related autoimmune conditions, further studies are needed to determine whether homocysteine represents a modifiable biomarker or therapeutic target in CLE-related cardiovascular risk. If a strong correlation between homocysteine levels and CLE disease activity is established, homocysteine could emerge as a valuable biomarker for assessing disease severity and progression, providing clinicians with a measurable indicator to monitor patients more effectively and enabling personalized treatment strategies tailored to individual metabolic and inflammatory profiles. Such an approach could enhance the precision of therapeutic interventions, improve patient outcomes, and potentially identify at-risk individuals earlier in the disease course.

Although the role of homocysteine has been extensively studied in cardiovascular disease and autoimmune conditions like SLE, its potential contribution to systemic inflammation and cardiovascular risk in CLE remains underexplored. Investigating homocysteine dynamics in CLE may uncover important connections between metabolic imbalance, immune activation, and vascular comorbidity in patients previously considered to have skin-limited disease.

Conflict of interest statement. None declared.

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