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Review Article

Cutaneous vasculopathy in microscopic colitis: the role of gut-derived endothelial toxins

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ABSTRACT

Microscopic colitis (MC) is a chronic inflammatory bowel disorder marked by persistent diarrhea and colonic mucosal inflammation. Emerging evidence suggests systemic manifestations, including cutaneous vasculopathy such as livedo reticularis and leukocytoclastic vasculitis, potentially driven by gut-derived endothelial toxins. However, the mechanisms linking MC to microvascular disorders remain poorly understood. This review examines the interplay between MC, gut dysbiosis, and systemic endothelial dysfunction, emphasizing the role of gut-derived toxins like lipopolysaccharides and microbial metabolites in vascular injury. A comprehensive literature search was conducted across PubMed, EMBASE, and Web of Science using predefined terms. Studies were appraised with standardized quality tools, and findings were categorized into endothelial toxin profiles, mechanisms of vascular injury, and clinical correlations. Emphasis was placed on studies using advanced techniques, such as metabolomics for toxin analysis, histopathology for vasculitis lesions, and imaging for vascular assessment. Evidence highlights a potential link between gut-derived toxins and systemic vascular effects in MC, though causality remains unproven. Variability in toxin profiles among MC patients and their correlation with cutaneous manifestations were noted. Key knowledge gaps include mechanisms of endothelial dysfunction, variability in toxin-mediated vascular injury, and lack of standardized diagnostic criteria for MC-associated vasculopathy. Further longitudinal and mechanistic studies are needed. Clarifying the role of endothelial toxins in MC-associated vasculopathy could lead to novel diagnostic biomarkers, therapeutic targets, and improved outcomes for patients with MC and its systemic vascular complications.

Keywords: Microscopic colitis, Cutaneous vasculopathy, Livedo reticularis, Leukocytoclastic vasculitis, Gut dysbiosis, Endothelial dysfunction, Lipopolysaccharides, Microbial metabolites, Vascular injury, Gut-skin connection

INTRODUCTION

Microscopic colitis (MC) is an increasingly recognized gastrointestinal disorder defined by chronic inflammation with persistent, non-bloody diarrhoea and mucosal inflammation. The incidence rate of microscopic colitis is estimated at 11.4 per 100,000 person-years, with a higher prevalence in females and individuals over 50.[1] The

diagnosis of MC is based on tissue samples obtained during routine colonoscopies. The pathogenesis of MC is thought to involve chronic T-cell activation, followed by cytokine release, which triggers an immune-mediated process that disrupts the gut mucosal barrier, resulting in chronic diarrhoea and inflammation of the colonic mucosa.[2]

The patient's history of chronic diarrhoea is essential in recognizing MC, as it differentiates it from other GI diseases, including inflammatory bowel disease, malignancy, and functional diarrhoea. Although considered a less severe inflammatory bowel disease (IBD), MC can significantly impact the quality of life, with its symptoms often persisting despite conventional treatments.[3] In addition to its gastrointestinal symptoms, MC has systemic manifestations, including joint pain, fatigue, and, more notably, cutaneous vasculopathy. Microscopic colitis may share immune-mediated pathways with cutaneous vasculitis, highlighting the need for multidisciplinary approaches to diagnosis and management.

Livedo reticularis and leukocytoclastic vasculitis, among other vasculopathies, are common systemic manifestations of inflammatory conditions, including microscopic colitis (MC). The pathology of these conditions is currently not fully understood but is thought to arise from the interplay of immune dysregulation, endothelial dysfunction, and inflammatory mediator release. Livedo reticularis manifests due to compromised blood flow in cutaneous micro vessels, leading to the characteristic net-like skin discoloration.[4] This condition is often associated with underlying systemic disorders, as its appearance can fluctuate with changes in systemic blood flow.

In contrast, leukocytoclastic vasculitis is marked by immune complex deposition in small blood vessels, leading to vessel inflammation, neutrophil infiltration, and subsequent tissue damage.[5] Gut-derived toxins are essential in microvascular endothelial injury associated with microscopic colitis (MC). Bacterial endotoxins can translocate into circulation by compromising the intestinal barrier, triggering systemic inflammation and endothelial dysfunction through toll-like receptor activation.[6] These findings suggest that gut-derived endotoxins may link microscopic colitis to cutaneous inflammatory vasculopathies such as livedo reticularis and leukocytoclastic vasculitis.

This review aims to synthesize current evidence exploring the interplay between microscopic colitis, gut dysbiosis, and systemic endothelial dysfunction, focusing on the role of gut-derived toxins such as lipopolysaccharides (LPS) and microbial metabolites. In the event of intestinal barrier compromise, these toxins bind to toll-like receptors, leading to downstream inflammatory signalling. Multimodal treatment is vital for managing the extra-intestinal manifestations of microscopic colitis because these systemic symptoms, such as joint pain or skin conditions, often require therapies beyond conventional gastrointestinal-focused treatments. Addressing these manifestations can improve overall patient well-being and prevent complications from untreated systemic involvement. By synthesizing current evidence, we seek to establish a more explicit connection between MC and its systemic manifestations, particularly cutaneous vasculopathy. Understanding these links could pave the way for novel therapeutic strategies and a more holistic approach to managing MC and its related complications.

REVIEW

The literature search used electronic databases such as PubMed, EMBASE, and Web of Science. The search strategy included keywords such as "microscopic colitis," "cutaneous vasculopathy," "gut-derived toxins," "endothelial toxins," "livedo reticularis," "leukocytoclastic vasculitis," and "inflammatory bowel disease," either individually or in combination. Boolean operators (AND/OR) were used to ensure comprehensive coverage. Filters were applied to limit the search to human studies, review articles, case reports, systematic reviews, and randomized controlled trials.

Inclusion criteria focused on articles addressing microscopic colitis (MC) and inflammatory bowel disease (IBD) with cutaneous or systemic vascular manifestations. English-only publications were selected based on their titles and abstracts. Priority was given to studies exploring the mechanisms of endothelial dysfunction, the role of gut-derived toxins, and clinical presentations of livedo reticularis or leukocytoclastic vasculitis. Articles discussing pathophysiological linkages of IBD and cutaneous manifestations were also included. Citations from these articles were reviewed for relevance. Studies unrelated to MC or IBD, endothelial toxins, or vasculopathy, as well as those lacking sufficient methodological rigor or data, were excluded from the review.

The quality of the articles was assessed based on study design, sample size, and methodology. Data was systematically collected on key topics, including gut-derived toxins, microvascular injury, and cutaneous outcomes. Findings were summarized and categorized into endothelial toxin profiles, vascular injury mechanisms, and clinical correlations with dermatological manifestations. Additional focus was given to studies utilizing advanced analytical techniques, such as metabolomics for toxin characterization, histopathology for vasculitic lesions, and imaging modalities for vascular assessment. Gaps in current understanding were also identified to highlight areas for future research.

Pathophysiology of microscopic colitis and vascular complications

Microscopic colitis (MC) is characterized by microscopic inflammation in the colon, induced by the activation of

various inflammatory signalling pathways. A critical aspect of this immune response is the production of pro-inflammatory cytokines such as IL-17, NF-κB, and IFN-γ.[7] These cytokines are produced by immune surveillance cells in the colonic mucosa, which are activated by intestinal antigens. A critical component of this inflammatory process in MC is the involvement of T helper cells. Specifically, Th1 and Th17 cells are upregulated in MC, producing pro-inflammatory cytokines such as IFN-γ and IL-17.[8] This cytokine-driven colonic inflammation disrupts the intestinal epithelium and has the potential to increase intestinal barrier permeability. This subsequently allows for antigenic products to enter the bloodstream and cause systemic effects.[6] The systemic spread of inflammatory cytokines in MC can contribute to the diverse clinical manifestations seen with the disease.

The systemic spread of inflammatory substances due to increased intestinal permeability is often referred to as "leaky gut syndrome" (LGS). Initially proposed to explain the systemic inflammation and autoimmune conditions associated with inflammatory bowel disease (IBD), LGS has been linked to diseases such as type 1 diabetes, multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis.[9] In addition to these autoimmune disorders, intestinal inflammation has also been associated with various cutaneous conditions. These include but are not limited to eczema, psoriasis, acne, and rosacea.[10] The effects of these conditions demonstrate how intestinal inflammation not only affects the intestinal epithelial lining but can also induce widespread systemic manifestations.

One metabolite implicated in the systemic effects of intestinal epithelial damage is lipopolysaccharide (LPS). LPS is a component of the outer membrane of gram-negative bacteria and is known to induce inflammatory cellular responses.[11] When the intestinal barrier is compromised due to chronic inflammation, LPS has the potential to enter the bloodstream and exert toxic effects on endothelial cells. Upon binding to toll-like receptors (TLRs) on endothelial cells, LPS activates intracellular inflammatory signalling pathways, including the NF-κB pathway.[12]

The NF-κB pathway can upregulate the expression of adhesion molecules. Specifically, ICAM and VCAM, are increased by this signalling cascade and promote the migration of leukocytes into the endothelial lining.[13,14] The migration of leukocytes into the endothelium through this pathway further exacerbates the inflammatory response and systemic vascular manifestations observed in MC. Increased expression of adhesion molecules can contribute to colonic inflammation. Recent studies have demonstrated increased expression of both ICAM-3 and VCAM-1 in biopsies of colonic mucosa from individuals with bowel inflammation.[15] The study suggests that the increased expression of these adhesion molecules, at both the cellular and vascular levels, may ultimately lead to inflammation in patients with IBD. Leukocyte infiltration facilitated by these adhesion molecules exacerbates the inflammatory response, increases vascular permeability, and triggers capillary damage.

When inflammatory cytokines bind to the VCAM-1 receptor, this activates the downstream effects of Rac1, which subsequently activates NADPH oxidase 2.[16] NADPH oxidase 2 and its role in oxidation formation can create reactive oxygen species (ROS) which can ultimately induce endothelial cell damage. Numerous studies have linked oxidative stress, a secondary effect of increased ROS, to the progression of various microvascular and macrovascular diseases.[17] Overall, as inflammatory mediators enter the bloodstream, they have the potential to affect vascular integrity and cause endothelial cell damage.

The vascular system is essential in the systemic inflammatory responses observed in MC, as inflammatory components initially located in the colonic mucosa can spread to distant sites after entering the bloodstream. Overall, studies of vascular inflammation and endothelial dysfunction have been associated with higher rates of systemic vascular complications.[18] Endothelial damage caused by these inflammatory markers in the vasculature has the potential to disproportionately affect organs with higher blood flow, such as the skin.

This may be one of the reasons for the cutaneous vasculopathies associated with MC. The parallel between gut-mediated microvascular injury and cutaneous vasculopathy demonstrates the widespread impact of intestinal inflammation on overall health. Once inflammatory cytokines and metabolites enter the systemic circulation, they can damage blood vessels throughout the body, including the skin. These systemic effects highlight the need to manage gut inflammation effectively to prevent widespread endothelial damage and its associated complications.

Cutaneous manifestations of vasculopathy in microscopic colitis

The systemic increase in inflammatory markers observed in microscopic colitis has been linked to various cutaneous manifestations, including livedo reticularis and leukocytoclastic vasculitis. The distinctive cone-shaped structure of cutaneous vasculature contributes to the presentation of livedo reticularis. These structures feature prominent venous regions at the margins of each cone. When blood flow in arteries and veins diminishes, the draining veins become more visible, resulting in livid discoloration and the characteristic closed-ring patterns.[19]

Livedo reticularis is a complex phenomenon often associated with temperature changes or systemic disease. It results from vasoconstriction, leading to blood stasis in dermal venules and a subsequent reduction in blood supply to skin arterioles.[19,20] These findings suggest that microvascular disruption is a key component of its underlying pathophysiology.

Consequently, any condition that impairs cutaneous blood flow can produce a livedo pattern, serving as a visible marker of systemic immune dysregulation. This observation raises the possibility of a connection between livedo reticularis and microscopic colitis. However, no studies have directly explored the prevalence of livedo reticularis among patients with microscopic colitis.

Leukocytoclastic vasculitis, a hypersensitivity vasculitis targeting post-capillary venules, has also been associated with inflammatory bowel disease (IBD).[21] Its pathogenesis involves immune complex formation, complement activation, and the subsequent release of inflammatory cytokines. Recognizing and addressing leukocytoclastic vasculitis early is crucial, as its clinical presentation can vary widely. Ford et al, emphasize the importance of thorough patient histories and comprehensive medical evaluations in diagnosing atypical presentations of IBD and leukocytoclastic vasculitis.

These steps are particularly important because histological findings may differ based on biopsy timing, and preliminary laboratory results can often appear unremarkable.[22,23] In patients with microscopic colitis or other gastrointestinal disorders, early identification and treatment of leukocytoclastic vasculitis are essential to prevent long-term complications.

The role of gut-derived toxins, such as lipopolysaccharides (LPS), in cutaneous vascular inflammation highlights the importance of considering gastrointestinal diseases when evaluating the causes of cutaneous vasculopathy.[24] Rigoni et al demonstrated that elevated LPS levels significantly upregulate toll-like receptor 4 (TLR4) and Interferon Gamma (IFN-γ) transcripts, leading to epidermal thickening, hyperkeratosis, abscess formation, and dermal infiltrates.[25] These findings suggest that TLR4 and IFN-γ play critical roles in initiating cutaneous vascular inflammation.

Further investigation into TLR4 and IFN-γ dysregulation could help identify patients predisposed to vasculopathy. Notably, IFN-γ has been identified as the predominant cytokine upregulated in microscopic colitis, supporting a potential link between microscopic colitis and various cutaneous manifestations.[26] Understanding systemic immune dysregulation in microscopic colitis could provide valuable insights for the development of targeted therapies. Nevertheless, the mechanistic relationship between microscopic colitis and skin vasculopathy remains poorly understood, underscoring the need for further research.

Emerging evidence and knowledge gaps

Lipopolysaccharides (LPS), recognized by toll-like receptors (TLRs), are significant contributors to low-grade endotoxemia, impacting various cell types such as leukocytes, platelets, and endothelial cells. These effects result in inflammation and clot formation. Recent studies have identified LPS in atherosclerotic arteries but not in healthy arteries, suggesting a potential predisposition to vascular disease in individuals with underlying endothelial dysfunction.[27] This finding underscores the intricate relationship between gut-derived toxins and endothelial dysfunction in systemic diseases, emphasizing the need for further research into these mechanisms.

Juvenile dermatomyositis (JDM) exemplifies a microvascular disorder characterized by endothelial dysfunction and associated skin vasculopathy. Studies suggest that the pathophysiological mechanisms in JDM may extend to the gastrointestinal tract in affected individuals.[28] The skin manifestations in JDM may reflect mechanisms similar to those underlying the cutaneous effects observed in microscopic colitis. Similarly, a case reported by Nassani et al, identified cutaneous vasculopathy as the initial indicator of Crohn's disease, preceding gastrointestinal symptoms.[23]

These examples highlight the potential link between gastrointestinal inflammation and cutaneous vascular disorders, emphasizing the importance of further investigation into the role of gut-derived toxins in endothelial function. Understanding this relationship could yield valuable insights into the pathogenesis and treatment of systemic diseases involving both gastrointestinal and cutaneous manifestations.

Microscopic colitis (MC) typically presents with a variable disease course and nonspecific symptoms, ranging from mild to severe, often mimicking irritable bowel syndrome or other gastrointestinal disorders. Diagnosis requires histological assessment of multiple biopsy sites due to the nonspecific nature of symptoms.[3,29] Limited awareness of the disease's presentation and pathophysiology often leads to its omission from differential diagnoses, particularly in cases with cutaneous involvement.

Cutaneous vasculopathy, such as livedoid vasculopathy, presents significant diagnostic challenges in MC due to overlapping features with other skin disorders.[30] These challenges, compounded by a limited understanding of both MC and its associated cutaneous manifestations, hinder accurate diagnosis and research into dermatological aspects of the disease. Diagnostic approaches remain complex due to the overlapping clinical and histological features of cutaneous and vascular disorders. However, combining clinical indicators such as medication history and rash distribution with biopsy and histological findings can support diagnosis.[30] Endothelial toxins play a central role in triggering inflammatory responses and causing endothelial damage. This process is likely mediated by TLR4 and IFN-γ, which have been implicated in initiating MC-related vasculopathy.[26] Although literature suggests a potential connection between endothelial toxins and MC-related vasculopathy, the limited understanding of the underlying mechanisms poses challenges for further research. Gut-skin vascular interactions in MC patients are particularly challenging to diagnose, often delaying

treatment and leading to worse health outcomes. These interactions can also have systemic effects, underscoring the necessity for early intervention. For instance, Nassani et al documented a case where gut-skin vascular involvement in Crohn's disease led to delayed treatment due to multiple differential diagnoses.[23] Similarly, the clinical presentation of MC often mimics other gastrointestinal diseases, increasing the risk of misdiagnosis and inappropriate treatment.

Further research is essential to better understand the relationship between gut-derived toxins, endothelial dysfunction, and cutaneous vasculopathies in MC. Improved insights could inform the development of effective care plans, standardize diagnostic approaches, and ultimately improve clinical outcomes for patients with gut-skin vascular interactions.

FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

Future research regarding the relationship between gut-derived toxins and cutaneous vasculopathy in MC is promising. Longitudinal cohort studies could help clarify how changes in gut toxin levels correlate with the onset of cutaneous symptoms, providing deeper insights into disease progression.[24] In addition to longitudinal studies, randomized controlled trials are essential for assessing microbiome-modulating therapies aimed at alleviating both gastrointestinal and cutaneous manifestations of MC.

Mechanistic studies utilizing animal models also have the potential to provide insight to the molecular pathways linking specific gut toxins, such as those from Clostridium difficile, to vascular changes.[31] Additionally, Mendelian randomization studies may help infer causal relationships between gut microbiota composition and cutaneous symptoms. This has the potential to help identify specific microbial taxa involved in the pathogenesis of the systemic manifestations of the disease.[32]

Integrating these research approaches with advanced techniques like metabolomics and immunological profiling could significantly improve diagnostic and therapeutic strategies. These studies could provide insights into the complex interplay between gut inflammation, microbiome alterations, and skin manifestations in patients with MC. These study methods could improve the understanding of the complex mechanisms underlying the systemic manifestations of MC and potentially lead to targeted interventions that address both the gastrointestinal and cutaneous symptoms of MC. Investigating biomarkers that indicate endothelial injury and vascular inflammation is essential to understanding the connection between gut-derived toxins and cutaneous vasculopathy in microscopic colitis. C-reactive protein and white blood cell counts are well-established markers of systemic inflammation linked to endothelial dysfunction.

Other biomarkers include trimethylamine N-oxide (TMAO), a metabolite produced by gut microbiota, and fecal calprotectin, which have been associated with endothelial and coronary microvascular dysfunction in patients with IBD.[33,34] These inflammatory markers could be utilized to develop more sensitive and specific diagnostic protocols for microscopic colitis, potentially allowing for earlier detection and intervention.

Validating these biomarkers within the specific context of microscopic colitis is necessary for a deeper understanding of how gut-derived toxins may contribute to cutaneous vasculopathy. This validation could lead to improved diagnostic accuracy and treatment strategies. Furthermore, understanding the role of these biomarkers might offer insights into the pathophysiological mechanisms underlying microscopic colitis. Ultimately, this research could enhance clinical outcomes by facilitating targeted therapies.

Interventions targeting gut-derived toxins show promise in mitigating systemic endothelial injury. Probiotics such as *Pediococcus acidilactici*, *Enterococcus faecium*, and *Escherichia coli* Nissle 1917 can modulate gut microbiota and enhance gut barrier function, potentially reducing the translocation of harmful toxins into the bloodstream.[35,36]

Assessing the efficacy of treatments that integrate microscopic colitis management with therapies for cutaneous vasculopathy is crucial to treating the systemic manifestations of the disease. Budesonide, a first-line treatment for MC, not only induces clinical remission but may also reduce systemic inflammation.[37] Dietary interventions such as the specific carbohydrate diet and low-FODMAP diet can also help manage MC symptoms by diminishing systemic inflammation.

Future research should optimize therapies, determine appropriate dosages and treatment durations, and assess their impact on endothelial function and inflammation markers. Evaluating the synergistic effects of these interventions will be essential for improving outcomes for patients suffering from both conditions. Such comprehensive approaches could lead to more effective management strategies for microscopic colitis and associated cutaneous vasculopathy. A comprehensive approach is essential for developing diagnostic protocols to evaluate vasculopathy manifestations in microscopic colitis patients. This should include clinical assessments and histological confirmation via colonoscopy with random biopsies. Laboratory tests for systemic inflammation and endothelial injury markers such as CRP, ESR, CBC, VEGF, and TMAO may also be necessary.[3,38] Imaging studies like Doppler ultrasound or MRI angiography can assess vascular involvement, while skin biopsies may confirm vasculitis in significant cases. The protocol should evaluate treatment efficacy, focusing on budesonide as the first-line therapy for MC. Future research should aim to standardize assessment criteria and explore less invasive diagnostic methods. Identifying

novel biomarkers and developing standardized follow-up protocols tailored to individual patient needs are crucial steps. These efforts are vital for improving care and outcomes for individuals affected by microscopic colitis and associated vasculopathy.

CONCLUSION

Microscopic colitis (MC) has recently been recognized not only as a gastrointestinal disorder but also as a condition with significant systemic effects, particularly with cutaneous manifestations. The dysfunctional immune response in MC, caused by the activation of inflammatory cytokines and the production of gut-derived toxins such as lipopolysaccharides (LPS), leads to endothelial dysfunction and the development of cutaneous vasculopathies. These include livedo reticularis and leukocytoclastic vasculitis. These vascular manifestations of MC show the complex interaction between gastrointestinal inflammation and larger systemic outcomes. The gastrointestinal-derived toxins have the potential to damage endothelial cells and lead to cutaneous manifestations.

Emerging evidence suggests that cytokines like IFN-γ, adhesion molecules, and microbial-derived toxins contribute significantly to endothelial damage. Although the exact mechanism between MC and cutaneous vascular disorders is not fully understood, integrating gut-targeted therapies with dermatological treatments offers promising avenues for patient care. Future research should focus on elucidating these interactions and developing targeted interventions to improve outcomes for individuals with MC. Longitudinal cohort studies, randomized controlled trials, mechanistic models, and Mendelian randomization studies could offer valuable insights into how gastrointestinal inflammation in MC contributes to disease progression.

Future integrated therapeutic strategies for MC should address dietary triggers (e.g., low fibre, low fat, reduced caffeine, gluten, and sugar) and standard treatments such as antidiarrheals, steroids like budesonide, bile acid blockers, and immunosuppressants. Effective management of dermatological manifestations, including warming measures for livedo reticularis and corticosteroids for leukocytoclastic vasculitis, further highlights the need for a comprehensive care strategy.

Personalized therapies targeting gut-derived endothelial toxins and inflammatory pathways, supported by interdisciplinary teams, can provide tailored solutions to multisystem complications. Nutritionists, dermatologists, and gastroenterologists must collaborate to optimize outcomes, leveraging dietary management and advanced therapies like biologics. Challenges, including variable MC presentation and multi-specialist coordination, highlight the need for research into MC staging and case management systems. Utilizing telehealth can also facilitate access to specialists and ensure continuous care.

Future studies should focus on the gut-skin axis to develop novel, personalized protocols for managing MC and its vascular complications, ultimately improving patient quality of life. In the future, a more comprehensive understanding of microscopic colitis (MC) and its connection to the gut-skin axis is essential for fully elucidating the cutaneous manifestations of the disease. Advancing research in this area could open the door to more effective therapeutic strategies, with the potential to significantly improve long-term outcomes and enhance the quality of life for patients with MC.

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