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MODERN PERSPECTIVES ON THE ETIOLOGY AND PATHOGENESIS OF HEMORRHAGIC VASCULITIS

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Abstract:

Hemorrhagic vasculitis, also known as IgA vasculitis, is a systemic small-vessel inflammatory disease characterized by the deposition of immunoglobulin A (IgA)-containing immune complexes in the vascular walls. Despite significant advances in medical science, the exact etiology of the disease remains incompletely understood. Current evidence suggests that genetic predisposition, infectious agents, environmental triggers, and immune dysregulation play crucial roles in the development of the disease. This article reviews contemporary concepts regarding the etiology and pathogenesis of hemorrhagic vasculitis, focusing on the mechanisms of IgA immune complex formation, endothelial injury, inflammatory responses, and the involvement of cytokines and complement pathways. Understanding these pathogenic mechanisms is essential for improving diagnostic approaches and developing targeted therapeutic strategies for patients with hemorrhagic vasculitis.

Keywords: Hemorrhagic vasculitis; IgA vasculitis; Henoch–Schönlein purpura; etiology; pathogenesis; immune complexes; immunoglobulin A; endothelial dysfunction; inflammation; cytokines; complement system; autoimmune mechanisms; vascular injury; nephritis; biomarkers.

INTRODUCTION. Hemorrhagic vasculitis, currently referred to as IgA vasculitis (IgAV), is the most common form of systemic vasculitis affecting small blood vessels. The disease is characterized by the deposition of immunoglobulin A (IgA)-dominant immune complexes within the walls of small vessels, leading to inflammation and vascular damage. Clinically, IgA vasculitis is manifested by palpable purpura, arthralgia or arthritis, gastrointestinal involvement, and renal complications of varying severity. Although the disease predominantly affects children, it may also occur in adults, where it often presents with a more severe clinical course and a higher risk of long-term complications.

The incidence of hemorrhagic vasculitis varies across different geographical regions and age groups, with the highest prevalence observed among children between the ages of 3 and 15 years. Despite decades of research, the exact etiology of the disease remains incompletely understood. Current evidence suggests that hemorrhagic vasculitis develops as a result of a complex interaction between genetic susceptibility, environmental exposures, infectious triggers, and abnormalities of the immune system. Upper respiratory tract infections, particularly those caused by streptococcal and viral pathogens, are frequently reported as preceding events in disease onset. In addition, certain medications, vaccinations, food allergens, and environmental factors have been implicated as potential triggers.

Recent advances in immunology and molecular medicine have significantly improved our understanding of the pathogenic mechanisms underlying hemorrhagic vasculitis. A central role is attributed to the abnormal glycosylation of IgA1 molecules, which promotes the formation of circulating immune complexes. These complexes accumulate within vessel walls and target organs, particularly the skin, kidneys, gastrointestinal tract, and joints. Their deposition activates inflammatory pathways, including complement system activation, recruitment of neutrophils, and release of pro-inflammatory cytokines, ultimately resulting in endothelial dysfunction and tissue injury.

Growing evidence also highlights the importance of genetic factors in disease susceptibility and progression. Variations in genes involved in immune regulation, cytokine production, and complement activation may influence both disease development and clinical outcomes. Furthermore, studies have demonstrated the involvement of various inflammatory mediators, including interleukins, tumor necrosis factor-alpha (TNF-α), and chemokines, which contribute to the maintenance and amplification of vascular inflammation.

Understanding the modern concepts of hemorrhagic vasculitis etiology and pathogenesis is essential for the development of improved diagnostic tools, prognostic biomarkers, and targeted therapeutic interventions. Advances in the identification of molecular pathways involved in disease progression may facilitate the

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implementation of personalized treatment strategies and improve long-term patient outcomes.

The aim of this article is to review contemporary perspectives on the etiology and pathogenesis of hemorrhagic vasculitis, with particular emphasis on immunological mechanisms, genetic factors, endothelial injury, and the role of inflammatory mediators in disease development and progression.

LITERATURE REVIEW. Hemorrhagic vasculitis, also known as IgA vasculitis (IgAV) or Henoch–Schönlein purpura, has been extensively studied since its first clinical description in the nineteenth century. Early investigations primarily focused on the clinical manifestations of the disease, including palpable purpura, joint involvement, gastrointestinal symptoms, and renal complications. However, advances in immunology and molecular biology have significantly expanded the understanding of its etiology and pathogenesis.

One of the most widely accepted theories regarding the pathogenesis of IgA vasculitis is the abnormal immune response hypothesis. Researchers have demonstrated that patients with IgA vasculitis exhibit increased levels of galactose-deficient IgA1 (Gd-IgA1), which plays a central role in disease development. According to studies conducted by Suzuki et al. and Novak et al., aberrant glycosylation of IgA1 molecules results in the formation of pathogenic immune complexes. These complexes accumulate in the walls of small blood vessels and trigger inflammatory reactions that lead to vascular damage.

Several studies have emphasized the role of infectious agents as important triggers of hemorrhagic vasculitis. Upper respiratory tract infections caused by Streptococcus species, influenza viruses, adenoviruses, parvovirus B19, and other pathogens have frequently been associated with disease onset. Pillebout and Thervet reported that approximately half of patients develop symptoms shortly after an infectious episode, suggesting a strong relationship between microbial antigens and immune activation. More recently, researchers have investigated the association between SARS-CoV-2 infection and the development of IgA vasculitis, with several case reports and clinical studies indicating a possible link between COVID-19-related immune dysregulation and vasculitic manifestations.

Genetic susceptibility has also been recognized as an important factor in disease pathogenesis. Genome-wide association studies have identified multiple genetic loci associated with immune regulation, complement activation, and mucosal immunity. Variations in human leukocyte antigen (HLA) genes, particularly HLA-DRB1 and HLA-B alleles, have been linked to increased susceptibility to IgA-mediated disorders. Furthermore, polymorphisms in genes encoding cytokines and complement proteins may influence disease severity and progression.

The complement system has emerged as another significant contributor to vascular injury in IgA vasculitis. Historically, the disease was considered independent of complement activation; however, recent investigations have demonstrated the involvement of the alternative and lectin complement pathways. Elevated levels of complement activation products, including C3a, C5a, and mannose-binding lectin, have been detected in affected patients. These findings suggest that complement-mediated inflammation contributes to endothelial damage and organ involvement, particularly in patients with nephritis.

Numerous studies have examined the role of inflammatory cytokines in disease progression. Increased serum concentrations of interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-17 (IL-17), tumor necrosis factor-alpha (TNF-α), and transforming growth factor-beta (TGF-β) have been reported in active disease stages. These cytokines promote leukocyte recruitment, endothelial activation, and persistent inflammation, thereby exacerbating vascular injury. The identification of these inflammatory mediators has generated interest in the development of targeted biological therapies for severe or refractory cases.

RESULTS. The analysis of contemporary scientific literature demonstrates that hemorrhagic vasculitis (IgA vasculitis) is a multifactorial immune-mediated disease characterized by complex interactions between genetic predisposition, environmental factors, infectious triggers, and immune dysregulation. The reviewed studies consistently identify abnormal IgA1 glycosylation as the central pathogenic mechanism leading to the formation of circulating immune complexes and subsequent vascular inflammation.

The findings indicate that infectious agents remain the most common triggering factors associated with disease onset. Upper respiratory tract infections caused by bacterial and viral pathogens have been reported in a significant proportion of patients prior to the appearance of clinical symptoms. Recent studies also suggest a potential association between SARS-CoV-2 infection and the development of IgA vasculitis, highlighting the role of immune activation in disease initiation.

A substantial body of evidence supports the involvement of genetic factors in disease susceptibility. Variations in genes regulating immune responses, cytokine production, and complement activation have been associated with an increased risk of developing

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hemorrhagic vasculitis. These genetic factors may contribute not only to disease occurrence but also to the severity of organ involvement and long-term prognosis.
The literature review further reveals that endothelial dysfunction plays a critical role in the progression of vascular injury. Activated neutrophils release proteolytic enzymes, reactive oxygen species, and inflammatory mediators that damage vascular endothelium. This process increases vascular permeability, leading to the characteristic manifestations of palpable purpura, edema, and tissue inflammation.
Complement system activation has emerged as an important pathogenic mechanism. Recent investigations demonstrate that the lectin and alternative complement pathways contribute significantly to endothelial damage. Elevated concentrations of complement activation products have been identified in patients with active disease, particularly those with renal involvement. These findings suggest that complement-mediated inflammation may serve as a potential therapeutic target in future treatment strategies.
Inflammatory cytokines have also been shown to play a major role in disease activity. Increased serum levels of IL-6, IL-8, IL-17, TNF-α, and other pro-inflammatory mediators were consistently observed in patients during active stages of the disease. The magnitude of cytokine elevation was positively correlated with disease severity and the extent of organ involvement.

Table 1. Major Etiological and Pathogenetic Factors in Hemorrhagic Vasculitis

Factor	Mechanism of Action	Clinical Significance
Infectious agents (bacteria, viruses)	Trigger abnormal immune response and IgA production	Initiation of disease episodes
Genetic predisposition	Influences immune regulation and complement activation	Increased susceptibility and disease severity
Abnormal IgA1 glycosylation	Formation of pathogenic immune complexes	Central mechanism of vasculitis development
Immune complex deposition	Accumulation in vessel walls and tissues	Vascular inflammation and organ damage
Complement activation	Endothelial injury and inflammatory amplification	Increased disease activity and nephritis risk
Cytokine overproduction	Enhancement of inflammatory responses	Progression of vascular injury
Endothelial dysfunction	Increased vascular permeability and tissue damage	Development of purpura and edema
Environmental triggers	Immune system stimulation	Disease recurrence and exacerbation

The reviewed evidence demonstrates that the skin is the most frequently affected organ, followed by the gastrointestinal tract, joints, and kidneys. Palpable purpura remains the hallmark clinical manifestation and is present in nearly all patients. Gastrointestinal involvement ranges from mild abdominal pain to severe complications such as intestinal bleeding and intussusception. Joint manifestations are generally transient and self-limiting.
Renal involvement represents the most clinically significant complication of hemorrhagic vasculitis. Studies indicate that nephritis develops in approximately 20–50% of patients, with severity varying from isolated microscopic hematuria to progressive glomerulonephritis. Patients exhibiting persistent proteinuria and severe histopathological changes demonstrate a higher risk of chronic kidney disease. Consequently, early detection and monitoring of renal manifestations remain essential for improving long-term outcomes.
The findings also reveal growing interest in novel biomarkers for disease diagnosis and prognosis. Elevated levels of galactose-deficient IgA1, complement activation products, and inflammatory cytokines have shown promising diagnostic and prognostic value. These biomarkers may contribute to earlier diagnosis, better disease monitoring, and the development of personalized treatment approaches.
The analyzed literature supports the concept that hemorrhagic vasculitis results from a complex interaction between immunological, genetic, infectious, and environmental factors. The identification of these mechanisms provides important insights into disease pathogenesis and may facilitate the development of targeted therapeutic interventions aimed at reducing vascular inflammation and preventing long-term organ damage.

DISCUSSION

The findings of the present literature review confirm that hemorrhagic vasculitis (IgA vasculitis) is a complex systemic inflammatory disorder whose development is

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influenced by multiple interacting factors. Although the disease has been recognized for more than a century, recent advances in immunology, molecular genetics, and vascular biology have significantly improved understanding of its underlying pathogenic mechanisms. The reviewed evidence demonstrates that abnormal immune regulation, particularly involving IgA-mediated immune responses, remains the cornerstone of disease pathogenesis.

One of the most important observations emerging from contemporary studies is the central role of galactose-deficient IgA1 (Gd-IgA1) in the initiation of vascular inflammation. Unlike normal IgA molecules, aberrantly glycosylated IgA1 exhibits altered antigenic properties, promoting the formation of circulating immune complexes. These complexes accumulate within small vessel walls and activate inflammatory pathways, leading to endothelial injury and tissue damage. The consistency of these findings across multiple studies suggests that Gd-IgA1 may serve as both a diagnostic biomarker and a potential therapeutic target.

The reviewed literature further highlights the importance of infectious agents as triggering factors. Respiratory tract infections are frequently reported before disease onset, indicating that microbial antigens may stimulate excessive IgA production and immune complex formation. However, the exact mechanisms by which infections initiate the disease remain incompletely understood. It is likely that infectious pathogens act as environmental triggers in genetically susceptible individuals rather than as direct causative agents. This concept supports the multifactorial nature of hemorrhagic vasculitis and explains the variability in disease presentation among patients.

Genetic predisposition has become an increasingly important area of investigation. Several studies have identified associations between specific HLA alleles and increased susceptibility to IgA vasculitis. Genetic variations affecting cytokine production, complement activation, and mucosal immune responses may influence both disease development and severity. Nevertheless, the current evidence suggests that no single genetic factor is sufficient to cause the disease independently. Instead, genetic susceptibility appears to interact with environmental and immunological factors, resulting in a complex pathogenic network.

Another significant aspect of disease pathogenesis is complement system activation. Traditionally, hemorrhagic vasculitis was considered primarily an immune-complex-mediated disorder; however, recent research has demonstrated the active participation of the complement cascade in vascular injury. Activation of the lectin and alternative complement pathways contributes to endothelial dysfunction, leukocyte recruitment, and amplification of inflammatory responses. The identification of complement-related mechanisms has expanded the understanding of disease progression and opened new possibilities for targeted therapeutic interventions.

Inflammatory cytokines represent another crucial component of the pathogenic process. Elevated concentrations of IL-6, IL-8, IL-17, TNF-α, and other mediators have been consistently observed in patients with active disease. These cytokines contribute to leukocyte activation, vascular permeability, and tissue destruction. Moreover, several studies have reported correlations between cytokine levels and disease severity, suggesting their potential value as biomarkers for monitoring disease activity and treatment response.

The results also emphasize the critical role of endothelial dysfunction in the clinical manifestations of hemorrhagic vasculitis. Vascular endothelial cells are directly exposed to deposited immune complexes and inflammatory mediators, leading to increased permeability and microvascular damage. This mechanism explains the development of palpable purpura, edema, and hemorrhagic lesions that characterize the disease. Persistent endothelial injury may further contribute to chronic inflammation and organ dysfunction.

Renal involvement remains the most important determinant of long-term prognosis in patients with hemorrhagic vasculitis. The reviewed studies indicate that nephritis develops in a substantial proportion of patients and represents the primary cause of long-term morbidity. The pathophysiological mechanisms underlying renal injury closely resemble those observed in systemic vascular lesions, involving immune complex deposition, complement activation, and inflammatory cell infiltration. Early identification of patients at risk for severe nephritis is therefore essential for preventing irreversible kidney damage and improving clinical outcomes.

Recent investigations have also explored the potential impact of emerging infectious diseases, particularly COVID-19, on the development of IgA vasculitis. Although available evidence remains limited, several reports suggest that SARS-CoV-2 infection may trigger abnormal immune responses leading to vasculitic manifestations. These observations provide additional support for the role of infectious stimuli in disease pathogenesis and warrant further investigation.

From a clinical perspective, the growing understanding of molecular and immunological mechanisms has important therapeutic implications. Traditional treatment approaches have primarily focused on

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symptom control through corticosteroids and immunosuppressive agents. However, advances in the understanding of disease pathways have stimulated interest in targeted therapies aimed at specific components of the immune response, including cytokine inhibitors, complement inhibitors, and biologic agents. Such therapies may offer improved efficacy while reducing treatment-related adverse effects.

Despite substantial progress, several challenges remain. The exact sequence of pathogenic events leading to disease initiation has not been fully elucidated, and reliable biomarkers for predicting disease severity and recurrence are still lacking. Furthermore, the heterogeneity of clinical manifestations complicates both diagnosis and treatment decisions. Future research should focus on identifying molecular predictors of disease progression, validating novel biomarkers, and evaluating targeted therapeutic strategies in large-scale clinical trials.

CONCLUSION. In summary, contemporary evidence indicates that hemorrhagic vasculitis is a multifactorial immune-mediated disease involving complex interactions between abnormal IgA responses, genetic susceptibility, infectious triggers, complement activation, cytokine-mediated inflammation, and endothelial dysfunction. Continued investigation of these mechanisms will contribute to improved diagnostic accuracy, personalized treatment approaches, and better long-term outcomes for affected patients.

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