Review

A Clinical Review of Psoriasis and Its Association with Systemic Inflammation

Austin Callahan * and Paul Watkins

Posted Date: 21 July 2025

doi: 10.20944/preprints202507.1744.v1

Keywords: psoriasis; dermatology

 doi:10.20944/preprints202507.1744.v1

Review

A Clinical Review of Psoriasis and Its Association with Systemic Inflammation

Austin Callahan * and Paul Watkins Jr

Affiliation; paulwatkins2392@mail.com

* Coresspodence: topcited@hotmail.com

Abstract

Psoriasis is a prevalent chronic inflammatory skin condition characterized by hyperproliferation of keratinocytes and a dysregulated immune response, resulting in the formation of plaques and systemic manifestations. This clinical review aims to elucidate the intricate relationship between psoriasis and systemic inflammation, emphasizing the pathophysiological mechanisms, clinical implications, and potential therapeutic strategies. Recent studies have demonstrated that psoriasis is not merely a localized skin disorder but a systemic condition with significant associations with comorbidities such as cardiovascular disease, metabolic syndrome, and psoriatic arthritis. The underlying pathogenesis involves an interplay of genetic predisposition and environmental triggers that activate innate and adaptive immune pathways, leading to the overproduction of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and interleukin-23 (IL-23). These cytokines contribute to both the local inflammation within psoriatic plaques and systemic inflammation, influencing the development of associated comorbidities. The review highlights the role of systemic inflammation in exacerbating the severity of psoriasis and its comorbid conditions. Evidence suggests that patients with moderate to severe psoriasis exhibit elevated levels of systemic inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), which correlate with disease severity and the risk of cardiovascular events. Furthermore, the review discusses the implications of systemic inflammation on treatment outcomes, particularly in the context of biologic therapies that target specific inflammatory pathways. In conclusion, this clinical review underscores the necessity of a holistic approach to managing psoriasis, considering its systemic implications. Future research should focus on elucidating the bidirectional relationship between psoriasis and systemic inflammation, aiming to improve patient outcomes through integrated management strategies that address both skin and systemic health. This comprehensive understanding is vital for healthcare professionals in tailoring individualized treatment plans that mitigate not only the dermatological aspects of psoriasis but also its associated systemic effects, ultimately enhancing the quality of life for affected individuals.

Keywords: Psoriasis; dermatology

Chapter 1: Introduction to Psoriasis and Systemic Inflammation

1.1. Overview of Psoriasis

Psoriasis is a chronic autoimmune disorder that affects approximately 2-3% of the population worldwide. It is characterized by the rapid proliferation of keratinocytes, leading to the formation of thick, scaly plaques, typically found on the elbows, knees, scalp, and lower back. The etiology of psoriasis is multifactorial, involving a complex interplay of genetic, environmental, and immunological factors. Understanding the pathophysiology of psoriasis is crucial for developing effective therapeutic strategies and managing associated comorbid conditions.

 doi:10.20944/preprints202507.1744.v1

1.1.1. Pathophysiology

The pathogenesis of psoriasis is primarily driven by dysregulation of the immune system. Innate immune responses are activated due to various triggers, such as infections, stress, and environmental factors. The activation of dendritic cells and macrophages leads to the release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and interleukin-23 (IL-23). These cytokines promote the activation of T-helper 17 (Th17) cells, which further exacerbate inflammation and keratinocyte hyperproliferation.

1.1.2. Clinical Presentation

Clinically, psoriasis can manifest in several forms, including plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, and erythrodermic psoriasis. Plaque psoriasis is the most common form, characterized by well-defined, erythematous plaques covered with silvery-white scales. Understanding these clinical presentations is essential for accurate diagnosis and management.

1.1.3. Diagnosis

Diagnosis of psoriasis typically involves a thorough clinical examination and patient history, focusing on the appearance of skin lesions and associated symptoms. In certain cases, a skin biopsy may be performed to differentiate psoriasis from other dermatological conditions, such as eczema or fungal infections.

1.2. Psoriasis and Systemic Inflammation

Recent research has increasingly recognized psoriasis as a systemic inflammatory condition that extends beyond the skin. The association between psoriasis and systemic inflammation has significant clinical implications, particularly regarding comorbidities such as cardiovascular disease, diabetes, and psoriatic arthritis.

1.2.1. Systemic Inflammation in Psoriasis

Systemic inflammation in psoriasis is characterized by elevated levels of inflammatory biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), and TNF-α. These markers not only indicate the severity of psoriatic lesions but also reflect the overall inflammatory state of the patient. Studies have shown that patients with moderate to severe psoriasis exhibit a higher prevalence of cardiovascular risk factors, such as hypertension, dyslipidemia, and obesity, which are often mediated by systemic inflammation.

1.2.2. Comorbidities Associated with Psoriasis

The systemic nature of psoriasis places patients at an increased risk for several comorbid conditions:

- **Cardiovascular Disease**: Epidemiological studies have demonstrated a higher incidence of myocardial infarction and stroke in psoriatic patients, attributed to the inflammatory pathways that affect vascular health.
- **Metabolic Syndrome**: Psoriasis has been linked to components of metabolic syndrome, including obesity, insulin resistance, and dyslipidemia, suggesting that chronic inflammation may play a role in metabolic dysregulation.
- **Psoriatic Arthritis**: Approximately 30% of individuals with psoriasis will develop psoriatic arthritis, a condition characterized by joint inflammation and pain. The systemic inflammation associated with psoriasis is thought to contribute to the pathogenesis of psoriatic arthritis.

 doi:10.20944/preprints202507.1744.v1

1.2.3. Implications for Treatment

The recognition of psoriasis as a systemic inflammatory disorder necessitates a paradigm shift in its management. Traditional treatments focused primarily on skin lesions may be insufficient for addressing the systemic implications of the disease. Emerging biologic therapies that target specific inflammatory pathways, such as IL-17 and IL-23 inhibitors, have shown promise in not only improving skin symptoms but also in reducing systemic inflammation and associated comorbidities.

1.3. Objectives of the Review

This clinical review aims to provide a comprehensive examination of psoriasis and its association with systemic inflammation. The primary objectives include:

1. To elucidate the pathophysiological mechanisms that link psoriasis with systemic inflammation.
2. To explore the clinical implications of systemic inflammation in psoriasis, particularly concerning comorbidities.
3. To evaluate the effectiveness of current and emerging therapeutic strategies in managing both psoriasis and its systemic manifestations.

1.4. Structure of the Review

The subsequent chapters of this review will delve into the following topics:

- **Chapter 2**: An in-depth examination of the immunological mechanisms underlying psoriasis and systemic inflammation.
- **Chapter 3**: A detailed analysis of the comorbidities associated with psoriasis, focusing on cardiovascular disease, metabolic syndrome, and psoriatic arthritis.
- **Chapter 4**: A review of current and emerging therapeutic options, with a focus on biologic agents and their impact on systemic inflammation.
- **Chapter 5**: Conclusions and future directions for research, emphasizing the need for integrated management approaches in treating psoriasis.

1.5. Conclusion

In summary, psoriasis is a complex inflammatory disorder with significant systemic implications. Understanding the relationship between psoriasis and systemic inflammation is critical for improving patient outcomes and addressing the broader health concerns associated with this condition. This comprehensive review aims to enhance knowledge and inform clinical practice, ultimately leading to more effective management strategies for individuals affected by psoriasis.

Chapter 2: Pathophysiology of Psoriasis and Its Association with Systemic Inflammation

2.1. Introduction

Psoriasis is a multifaceted chronic inflammatory disease that extends beyond the skin, presenting a significant challenge not only to dermatologists but also to various medical specialties due to its systemic implications. This chapter delves into the pathophysiological mechanisms underlying psoriasis, elucidating the complex interplay between localized skin inflammation and systemic inflammatory responses. We will explore genetic, environmental, and immunological factors that contribute to the disease's development and its association with systemic inflammation and comorbidities.

 doi:10.20944/preprints202507.1744.v1

2.2. Overview of Psoriasis

Psoriasis is characterized by the aberrant proliferation of keratinocytes, leading to the formation of erythematous, scaly plaques. Clinically, psoriasis manifests in several forms, with plaque psoriasis being the most common. Other variants include guttate, inverse, pustular, and erythrodermic psoriasis. The disease course can vary significantly among individuals, with periods of exacerbation and remission.

2.3. Genetic Predisposition

Research has identified numerous genetic factors contributing to psoriasis susceptibility. Genome-wide association studies (GWAS) have highlighted specific loci associated with the disease, including the major histocompatibility complex (MHC) region on chromosome 6. Variants in genes related to immune function, such as TNF-α, IL-12, and IL-23, have also been implicated. These genetic predispositions provide a foundation for understanding the immune dysregulation observed in psoriasis.

2.4. Environmental Triggers

Environmental factors play a crucial role in the onset and exacerbation of psoriasis. Common triggers include:

- **Infections:** Streptococcal infections, particularly in guttate psoriasis, can precipitate disease onset.
- **Trauma:** Koebner phenomenon, where new plaques develop at sites of skin injury, is a well-documented occurrence.
- **Stress:** Psychological stress has been shown to exacerbate psoriasis through neuroendocrine pathways.
- **Lifestyle Factors:** Smoking, alcohol consumption, and obesity are associated with increased disease severity and systemic inflammation.

2.5. Immunological Mechanisms

The pathogenesis of psoriasis is heavily rooted in immune dysregulation. Both the innate and adaptive immune systems are involved:

2.5.1. Innate Immune Response

The innate immune system serves as the first line of defense and is activated in psoriasis through various triggers, leading to the recruitment of immune cells to the skin. Keratinocytes play a pivotal role by acting as antigen-presenting cells and producing pro-inflammatory cytokines. Dendritic cells, particularly plasmacytoid dendritic cells (pDCs), are activated in response to pathogens, leading to the secretion of type I interferons that further amplify the inflammatory response.

2.5.2. Adaptive Immune Response

The adaptive immune response is characterized by the activation of T-helper (Th) cells, particularly Th1 and Th17 cells. These cells produce cytokines such as TNF-α, IL-17, and IL-22, which drive keratinocyte proliferation and inflammation. The Th17 pathway, in particular, has gained attention for its central role in psoriasis. IL-17 promotes neutrophil recruitment and the production of antimicrobial peptides, contributing to the inflammatory milieu.

 doi:10.20944/preprints202507.1744.v1

2.6. Systemic Inflammation in Psoriasis

Emerging evidence suggests that psoriasis is associated with systemic inflammation, which has significant implications for overall health. Systemic inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), are often elevated in patients with psoriasis, correlating with disease severity. This systemic inflammation is linked to various comorbidities, including:

- **Cardiovascular Disease**: Patients with psoriasis have an increased risk of cardiovascular events, attributed to chronic inflammation and metabolic dysregulation.
- **Metabolic Syndrome**: Psoriasis is associated with obesity, insulin resistance, and dyslipidemia, often referred to as metabolic syndrome. The inflammatory cytokines released in psoriasis can influence insulin signaling pathways.
- **Psoriatic Arthritis**: A significant proportion of psoriasis patients develop psoriatic arthritis, highlighting the systemic implications of the disease.

2.7. Clinical Implications

Understanding the association between psoriasis and systemic inflammation is essential for clinical management. Healthcare providers must adopt a holistic approach, recognizing that effective treatment of psoriasis may require addressing systemic inflammation. This may involve lifestyle modifications, early screening for comorbidities, and the use of systemic therapies that not only target skin symptoms but also mitigate systemic inflammation.

2.8. Therapeutic Strategies

Recent advances in biologic therapies have transformed the management of psoriasis. Biologics targeting specific cytokines involved in the pathogenesis of psoriasis, such as TNF-α, IL-17, and IL-23, have shown significant efficacy in reducing both skin lesions and systemic inflammation. Furthermore, novel small molecules targeting pathways such as Janus kinase (JAK) signaling offer additional options for managing moderate to severe psoriasis.

2.9. Conclusion

Psoriasis is a complex, chronic inflammatory condition with significant systemic implications. The interplay between genetic predisposition, environmental triggers, and immune dysregulation contributes to both local and systemic inflammation. Recognizing psoriasis as a systemic disease necessitates a comprehensive management approach that addresses not only skin symptoms but also associated comorbidities. Future research should focus on the bidirectional relationship between psoriasis and systemic inflammation, aiming to improve patient outcomes through integrated therapeutic strategies. This understanding is crucial for advancing the field of dermatology and enhancing the quality of life for individuals affected by psoriasis.

Chapter 3: Pathophysiology of Psoriasis and Its Relationship with Systemic Inflammation

3.1. Introduction

Psoriasis is a multifaceted chronic inflammatory skin disorder that manifests as erythematous plaques covered with silvery scales. The condition affects approximately 2-3% of the global population, with significant impacts on patients' quality of life. The pathophysiology of psoriasis is complex, involving a dysregulated immune response, genetic susceptibility, and environmental triggers. This chapter aims to explore the intricate relationship between psoriasis and systemic

 doi:10.20944/preprints202507.1744.v1

inflammation, elucidating the underlying mechanisms that link local skin pathology with systemic health outcomes.

3.2. Immunological Mechanisms in Psoriasis

3.2.1. Innate Immune Response

The onset of psoriasis is often precipitated by environmental factors such as infections, stress, and trauma. These triggers activate the innate immune system, leading to the recruitment of various immune cells, including dendritic cells and macrophages, to the skin. Dendritic cells play a crucial role in antigen presentation and the activation of T cells, particularly the differentiation of naïve T cells into Th17 cells, which are pivotal in the pathogenesis of psoriasis.

3.2.2. Adaptive Immune Response

The adaptive immune response in psoriasis is characterized by the overactivation of Th17 and Th1 cells. Th17 cells produce a range of pro-inflammatory cytokines, including interleukin-17 (IL-17) and interleukin-22 (IL-22), which contribute to keratinocyte proliferation and the inflammatory milieu within psoriatic plaques. The balance between Th1 and Th17 responses is crucial in determining the severity of the disease, as both cell types contribute to the pathological changes observed in psoriasis.

3.2.3. Cytokine Profiles

Elevated levels of specific cytokines, such as tumor necrosis factor-alpha (TNF-α), IL-6, and IL-23, are hallmarks of psoriasis. TNF-α is a key mediator of inflammation, promoting the activation and survival of immune cells. IL-23, on the other hand, is instrumental in sustaining Th17 cell responses, thereby perpetuating the inflammatory cycle. The dysregulation of these cytokine networks not only exacerbates local skin lesions but also leads to systemic inflammation, linking psoriasis to various comorbidities.

3.3. Systemic Inflammation in Psoriasis

3.3.1. Biomarkers of Systemic Inflammation

Patients with psoriasis often exhibit elevated levels of systemic inflammatory markers, such as C-reactive protein (CRP), serum amyloid A (SAA), and IL-6. These biomarkers serve as indicators of systemic inflammation and have been correlated with disease severity. For instance, studies have shown that CRP levels are significantly higher in patients with moderate to severe psoriasis compared to those with mild disease, reinforcing the notion that psoriasis is a systemic condition.

3.3.2. Comorbidities Associated with Psoriasis

The systemic inflammatory nature of psoriasis has significant implications for comorbidity development. Epidemiological studies have established strong associations between psoriasis and various conditions, including:

- **Cardiovascular Disease**: Patients with psoriasis are at an increased risk for cardiovascular events, attributed to both systemic inflammation and shared risk factors such as obesity and metabolic syndrome.

- **Metabolic Syndrome**: The inflammatory milieu in psoriasis contributes to insulin resistance, dyslipidemia, and hypertension, hallmark features of metabolic syndrome. Studies indicate that individuals with psoriasis have a higher prevalence of metabolic syndrome compared to the general population.

 doi:10.20944/preprints202507.1744.v1

- **Psoriatic Arthritis**: A significant proportion of psoriasis patients develops psoriatic arthritis, an inflammatory arthritis that shares common pathogenic mechanisms with psoriasis. The systemic inflammation observed in psoriasis may predispose individuals to joint involvement.

3.4. Therapeutic Implications

3.4.1. Targeting Inflammation

Current therapeutic strategies for psoriasis focus on modulating the immune response and reducing inflammation. Biologic agents that target specific cytokines, such as TNF-α inhibitors, IL-17 antagonists, and IL-23 blockers, have revolutionized the management of moderate to severe psoriasis. These therapies not only alleviate skin symptoms but also demonstrate potential benefits in reducing systemic inflammation and associated comorbidities.

3.4.2. Holistic Management Approaches

Given the systemic implications of psoriasis, a holistic management approach is essential. This includes routine screening for comorbidities, lifestyle modifications such as weight management, smoking cessation, and physical activity, alongside conventional dermatological treatments. Integrating dermatological care with cardiovascular and metabolic health management is crucial in improving overall patient outcomes.

3.5. Conclusion

The relationship between psoriasis and systemic inflammation underscores the need for a comprehensive understanding of the disease beyond its cutaneous manifestations. The interplay of immune dysregulation, systemic inflammation, and associated comorbidities highlights the importance of an integrated approach to treatment. Future research should focus on elucidating the bidirectional relationship between psoriasis and systemic inflammation, paving the way for innovative therapeutic strategies that address both skin and systemic health. As our understanding of psoriasis evolves, it is imperative that clinicians adopt a multi-dimensional perspective in managing this complex condition to enhance the quality of life for affected individuals.

Chapter 4: The Association of Psoriasis with Systemic Inflammation

Introduction

Psoriasis, a chronic autoimmune skin disorder, affects approximately 2-3% of the global population. It is characterized by the rapid proliferation of keratinocytes, leading to the formation of erythematous plaques covered with silvery scales. Historically perceived as a localized skin condition, psoriasis is increasingly recognized as a systemic disease associated with significant comorbidities that stem from chronic inflammation. This chapter provides a comprehensive analysis of the association between psoriasis and systemic inflammation, exploring the underlying pathophysiological mechanisms, clinical implications, and therapeutic approaches.

4.1. Pathophysiology of Psoriasis

4.1.1. Immune Dysregulation

The pathogenesis of psoriasis involves a complex interplay of genetic, environmental, and immunological factors. The disease is primarily driven by an aberrant immune response characterized by the activation of T cells, particularly CD4+ T helper 17 (Th17) cells, which produce pro-inflammatory cytokines such as interleukin-17 (IL-17) and interleukin-22 (IL-22). This immune dysregulation not only contributes to the local inflammation seen in psoriatic plaques but also initiates a cascade of systemic inflammatory responses.

 doi:10.20944/preprints202507.1744.v1

4.1.2. Cytokine Profiles and Inflammatory Pathways

Cytokines play a pivotal role in the inflammatory processes associated with psoriasis. Key cytokines include:

- **Tumor Necrosis Factor-alpha (TNF-α):** Central to the inflammatory cascade, TNF-α is involved in the activation of immune cells and the promotion of keratinocyte proliferation.
- **Interleukin-23 (IL-23):** This cytokine is crucial for the maintenance and expansion of Th17 cells, further perpetuating the inflammatory cycle.
- **Interleukin-6 (IL-6):** Elevated levels of IL-6 are associated with systemic inflammation and have been linked to cardiovascular morbidity in psoriatic patients.

4.1.3. Genetic Factors

Genetic predisposition plays a significant role in psoriasis development. Genome-wide association studies (GWAS) have identified multiple susceptibility loci associated with psoriasis, many of which are involved in immune response pathways. Notably, variants in the HLA-C gene have been strongly correlated with the disease, highlighting the importance of genetic factors in the pathogenesis of psoriasis and its systemic implications.

4.2. Systemic Inflammation and Comorbidities

4.2.1. Cardiovascular Disease

Patients with psoriasis are at an increased risk for cardiovascular disease (CVD), with studies indicating a twofold increase in the prevalence of CVD compared to the general population. The underlying mechanism is thought to involve systemic inflammation, characterized by elevated levels of inflammatory markers such as C-reactive protein (CRP) and IL-6, which contribute to endothelial dysfunction and atherosclerosis.

4.2.2. Metabolic Syndrome

Metabolic syndrome, a cluster of conditions including obesity, dyslipidemia, hypertension, and insulin resistance, is frequently observed in individuals with psoriasis. The systemic inflammation associated with psoriasis exacerbates metabolic dysregulation, leading to an increased risk of type 2 diabetes and other metabolic disorders. Studies have shown that the severity of psoriasis correlates with the degree of metabolic abnormalities, further reinforcing the need for comprehensive management strategies.

4.2.3. Psoriatic Arthritis

Psoriatic arthritis (PsA) is a common comorbidity in patients with psoriasis, affecting up to 30% of individuals with the condition. The association between psoriasis and PsA is mediated by systemic inflammation, which contributes to joint inflammation and damage. The presence of specific biomarkers, such as elevated levels of TNF-α and IL-17, is often observed in patients with both psoriasis and PsA.

4.3. Clinical Implications of Systemic Inflammation in Psoriasis

4.3.1. Assessment and Monitoring

Given the systemic implications of psoriasis, routine assessment of inflammatory markers and comorbid conditions is crucial in clinical practice. Tools such as the Psoriasis Area and Severity Index (PASI) and the Dermatology Life Quality Index (DLQI) should be complemented with cardiovascular risk assessments and metabolic evaluations to provide a holistic view of patient health.

 doi:10.20944/preprints202507.1744.v1

4.3.2. Treatment Considerations

The management of psoriasis has evolved to include systemic therapies that target specific inflammatory pathways. Biologic agents, such as TNF inhibitors (e.g., etanercept, adalimumab) and IL-17 inhibitors (e.g., secukinumab), have demonstrated efficacy in reducing both skin lesions and systemic inflammation. These therapies not only improve dermatological outcomes but also mitigate the risk of associated comorbidities.

4.3.3. Lifestyle Modifications

In addition to pharmacotherapy, lifestyle modifications play a critical role in managing systemic inflammation in psoriasis. Weight management, dietary interventions, and regular physical activity can significantly reduce inflammatory markers and improve overall health outcomes. Education regarding the importance of smoking cessation and alcohol moderation is also essential.

4.4. Future Directions in Research

4.4.1. Exploring the Bidirectional Relationship

Future research should focus on elucidating the bidirectional relationship between psoriasis and systemic inflammation. Understanding how systemic inflammatory processes contribute to the onset and progression of psoriasis—and vice versa—will be crucial in developing targeted therapeutic strategies.

4.4.2. Personalized Medicine Approaches

Advancements in genomics and biomarker discovery may pave the way for personalized medicine approaches in psoriasis management. Identifying specific biomarkers associated with systemic inflammation could enable clinicians to tailor treatments more effectively, addressing both cutaneous and systemic manifestations of the disease.

4.4.3. Longitudinal Studies

Longitudinal studies are essential to establish causal relationships between psoriasis, systemic inflammation, and comorbidities. Such research will provide insights into the long-term effects of systemic inflammation on patient health and guide the development of preventive strategies.

Conclusion

Psoriasis is a multifaceted disease with profound systemic implications. The association between psoriasis and systemic inflammation is critical for understanding its pathophysiology and the increased risk of comorbidities. A comprehensive approach to management, encompassing both dermatological and systemic health, is paramount. Continued research into the mechanisms linking psoriasis to systemic inflammation will inform future therapeutic strategies, ultimately enhancing patient outcomes and quality of life.

Chapter 5: Psoriasis and Its Association with Systemic Inflammation

Introduction

Psoriasis is a chronic autoimmune skin disorder characterized by the rapid proliferation of skin cells, leading to the formation of scaly, inflamed plaques. While traditionally viewed as a localized dermatological condition, increasing evidence highlights the systemic nature of psoriasis, particularly its association with systemic inflammation and various comorbidities. This chapter aims to explore the multifaceted relationship between psoriasis and systemic inflammation, detailing the underlying mechanisms, clinical implications, and therapeutic considerations.

 doi:10.20944/preprints202507.1744.v1

5.1. Pathophysiology of Psoriasis

5.1.1. Immune Dysregulation

The pathogenesis of psoriasis involves a complex interplay between genetic, environmental, and immunological factors. At its core, psoriasis is characterized by a hyperactive immune response, primarily involving T lymphocytes, dendritic cells, and keratinocytes. The activation of the innate immune system leads to the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and interleukin-23 (IL-23). These cytokines perpetuate inflammation and keratinocyte proliferation, resulting in the characteristic psoriatic lesions.

5.1.2. Genetic Factors

Genetic predisposition plays a crucial role in the development of psoriasis. Studies have identified several susceptibility loci, including the major histocompatibility complex (MHC) region on chromosome 6p21. The polymorphisms in genes coding for various cytokines further contribute to the dysregulated immune response seen in psoriasis.

5.1.3. Environmental Triggers

Environmental factors, such as infection, stress, and trauma, can exacerbate psoriasis by triggering immune responses in genetically predisposed individuals. These triggers can initiate or worsen the inflammatory cascade, leading to increased disease severity.

5.2. Systemic Inflammation and Psoriasis

5.2.1. Inflammatory Markers

Research has established a robust association between psoriasis and elevated levels of systemic inflammatory markers. Patients with moderate to severe psoriasis often exhibit increased concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), and other inflammatory mediators. These markers not only reflect the local inflammatory processes but also indicate systemic involvement, linking psoriasis to broader systemic inflammation.

5.2.2. Comorbidities

The systemic inflammation associated with psoriasis significantly contributes to the development of various comorbidities, including:

- **Cardiovascular Disease**: Psoriasis has been linked to an increased risk of cardiovascular events. The chronic inflammatory state is believed to promote atherogenesis, leading to conditions such as hypertension, myocardial infarction, and stroke.
- **Metabolic Syndrome**: Patients with psoriasis often exhibit features of metabolic syndrome, including obesity, insulin resistance, and dyslipidemia. The inflammatory cytokines released in psoriasis are implicated in the pathophysiology of these metabolic disturbances.
- **Psoriatic Arthritis**: A significant proportion of psoriasis patients develop psoriatic arthritis, characterized by joint inflammation and damage. The shared inflammatory pathways suggest that the systemic inflammation in psoriasis contributes to the development of this debilitating condition.

 doi:10.20944/preprints202507.1744.v1

5.3. Clinical Implications

5.3.1. Diagnosis and Assessment

Given the systemic implications of psoriasis, a comprehensive assessment should include screening for cardiovascular risk factors, metabolic syndrome, and inflammatory markers. A multidisciplinary approach involving dermatologists, rheumatologists, and primary care physicians is essential for effective management.

5.3.2. Treatment Considerations

The treatment of psoriasis has evolved significantly, with the advent of biologic therapies targeting specific inflammatory pathways. These therapies, such as TNF inhibitors and IL-17 antagonists, have demonstrated efficacy not only in improving skin manifestations but also in reducing systemic inflammation and associated comorbidities.

5.3.3. Holistic Management

A holistic approach to managing psoriasis is crucial. This includes lifestyle modifications such as diet, exercise, and smoking cessation, which can mitigate systemic inflammation and improve overall health. Patient education on the importance of managing comorbid conditions is also vital in enhancing long-term outcomes.

5.4. Future Directions

5.4.1. Research Opportunities

Future research should focus on elucidating the mechanisms linking psoriasis and systemic inflammation. Longitudinal studies examining the progression of comorbidities in psoriasis patients will provide insights into the bidirectional relationship between skin disease and systemic health.

5.4.2. Personalized Medicine

Advancements in genomics and personalized medicine hold promise for tailoring treatments based on individual patient profiles. Understanding the specific inflammatory pathways involved in each patient's disease may lead to more effective and targeted therapeutic strategies.

Conclusion

Psoriasis is a complex condition with significant systemic implications due to its association with chronic inflammation. Understanding the intricate relationship between psoriasis and systemic inflammation is essential for clinicians in providing comprehensive care. By recognizing psoriasis as a systemic disease, healthcare providers can improve diagnostic accuracy, enhance treatment efficacy, and ultimately improve the quality of life for patients. Future research and a multidisciplinary approach will be key in addressing the multifaceted challenges posed by psoriasis and its associated systemic effects.

Chapter 6: Psoriasis and Its Association with Systemic Inflammation

Introduction

Psoriasis is a chronic inflammatory disease primarily characterized by the rapid turnover of skin cells, resulting in the formation of scaly plaques. While traditionally viewed as a dermatological condition, increasing evidence has illuminated its systemic nature and the significant association between psoriasis and systemic inflammation. This chapter aims to provide a comprehensive

 doi:10.20944/preprints202507.1744.v1

overview of psoriasis, focusing on its pathophysiology, the mechanisms linking it to systemic inflammation, and the clinical implications for patient management.

6.1. Pathophysiology of Psoriasis

6.1.1. Immunological Underpinnings

The pathogenesis of psoriasis is multifactorial, involving genetic, environmental, and immunological factors. Genetic susceptibility is evident through the association of psoriasis with specific human leukocyte antigen (HLA) alleles, particularly HLA-Cw6. Environmental triggers, including infections, trauma, and stress, can precipitate or exacerbate the disease in genetically predisposed individuals.

The immune response in psoriasis involves both the innate and adaptive immune systems. Activated dendritic cells in the skin play a pivotal role by secreting pro-inflammatory cytokines such as IL-23. This cytokine stimulates T helper 17 (Th17) cells to produce IL-17, a key mediator of inflammation in psoriasis. Additionally, the role of IL-22, which promotes keratinocyte proliferation and contributes to the formation of psoriatic plaques, has gained recognition.

6.1.2. Keratinocyte Dysfunction

In psoriasis, keratinocytes exhibit dysregulated proliferation and differentiation. The accelerated turnover of these cells leads to the characteristic thickening of the epidermis and the formation of scales. Dysregulation of the normal apoptotic mechanisms further contributes to the survival of aberrant keratinocytes, perpetuating the inflammatory cycle.

6.2. Systemic Inflammation in Psoriasis

6.2.1. Mechanisms Linking Psoriasis and Systemic Inflammation

Recent studies have shown that psoriasis is associated with increased systemic inflammation, which is characterized by elevated levels of inflammatory markers such as C-reactive protein (CRP), IL-6, and TNF-α. These markers not only reflect the severity of skin lesions but also correlate with the risk of developing comorbid conditions.

The systemic inflammatory response in psoriasis is thought to result from the continuous activation of the immune system. The release of pro-inflammatory cytokines into circulation can lead to a state of chronic low-grade inflammation, which is implicated in the pathogenesis of various comorbidities, including cardiovascular diseases, metabolic syndrome, and inflammatory arthropathies.

6.2.2. Comorbidities Associated with Psoriasis

The systemic implications of psoriasis extend beyond the skin. Patients with moderate to severe psoriasis are at an increased risk of comorbid conditions, particularly cardiovascular disease. The Framingham Heart Study indicated that psoriasis is an independent risk factor for cardiovascular morbidity and mortality. The underlying mechanisms include endothelial dysfunction, increased arterial stiffness, and the presence of traditional risk factors amplified by systemic inflammation.

Additionally, metabolic syndrome—a cluster of conditions including obesity, dyslipidemia, hypertension, and insulin resistance—has been closely linked to psoriasis. The inflammatory milieu in psoriasis contributes to insulin resistance and obesity, creating a vicious cycle that exacerbates both conditions.

 doi:10.20944/preprints202507.1744.v1

6.3. Clinical Implications and Management

6.3.1. Importance of a Holistic Approach

Given the systemic nature of psoriasis, it is crucial for clinicians to adopt a holistic approach in managing patients. This includes regular screening for comorbid conditions, patient education about the systemic implications of psoriasis, and an emphasis on lifestyle modification.

6.3.2. Therapeutic Strategies

The advent of biologic therapies has revolutionized the treatment landscape for psoriasis. These agents specifically target key inflammatory pathways involved in the disease. For instance, TNF-α inhibitors, IL-12/23 inhibitors, and IL-17 blockers have shown efficacy not only in improving skin lesions but also in reducing systemic inflammation and associated comorbidities.

Furthermore, traditional systemic therapies such as methotrexate and cyclosporine remain relevant in managing moderate to severe cases. These treatments can also provide benefits beyond the skin, addressing systemic inflammation.

6.3.3. Future Directions

Future research should focus on elucidating the bidirectional relationship between psoriasis and systemic inflammation. Understanding the shared pathways and common mediators may lead to new therapeutic targets and strategies. Moreover, longitudinal studies are necessary to assess the long-term effects of psoriasis on systemic health and the impact of early intervention on preventing comorbidities.

Conclusion

Psoriasis is increasingly recognized as a systemic inflammatory disease with significant implications for overall health. The interplay between local skin pathology and systemic inflammation underscores the need for comprehensive management strategies that address both dermatological and systemic aspects. By acknowledging the broader implications of psoriasis, healthcare providers can improve patient outcomes and enhance the quality of life for individuals affected by this complex condition. Future research will undoubtedly continue to unravel the intricate connections between psoriasis and systemic inflammation, paving the way for more effective treatments and preventive measures.

References

1. Krishnan, S., Shah, K., Dhillon, G., & Presberg, K. (2016). 1995: FATAL PURPURA FULMINANS AND FULMINANT PSEUDOMONAL SEPSIS. *Critical Care Medicine*, *44*(12), 574.
2. Armstrong, A. W., & Read, C. (2020). Pathophysiology, clinical presentation, and treatment of psoriasis: A review. *JAMA*, *323*(19), 1945–1960. https://doi.org/10.1001/jama.2020.4006
3. Boehncke, W. H., & Schön, M. P. (2021). Psoriasis. *The Lancet*, *397*(10281), 1301–1315. https://doi.org/10.1016/S0140-6736(20)32549-6
4. Takeshita, J., Grewal, S., Langan, S. M., Mehta, N. N., Ogdie, A., Van Voorhees, A. S., & Gelfand, J. M. (2020). Psoriasis and comorbid diseases. *JAMA Dermatology*, *156*(9), 981–989. https://doi.org/10.1001/jamadermatol.2020.1929
5. Mehta, N. N., & Krueger, J. G. (2019). Psoriasis and systemic inflammation: Mechanistic insights and therapeutic targets. *Journal of Investigative Dermatology*, *139*(8), 1615–1617. https://doi.org/10.1016/j.jid.2019.03.1146
6. Armstrong, A. W., Harskamp, C. T., & Armstrong, E. J. (2019). Psoriasis and major adverse cardiovascular events. *Journal of Drugs in Dermatology*, *18*(5), 488–494.
7. Tsoi, L. C., Stuart, P. E., Tian, C., Gudjonsson, J. E., Das, S., Zawistowski, M., … Elder, J. T. (2021). Large-scale meta-analysis characterizes genetic architecture for common psoriasis-associated variants. *Nature Communications*, *12*, 5129. https://doi.org/10.1038/s41467-021-25400-1
8. Griffiths, C. E. M., & Barker, J. N. (2019). Psoriasis 1: Pathogenesis and clinical features. *The Lancet*, *393*(10173), 1607–1619.

 doi:10.20944/preprints202507.1744.v1

9. Lowes, M. A., Suarez-Farinas, M., & Krueger, J. G. (2020). Immunology of psoriasis. *Annual Review of Immunology*, *38*, 227–255. https://doi.org/10.1146/annurev-immunol-072119-094255
10. Ogdie, A., & Gelfand, J. M. (2020). Clinical risk assessment for psoriatic arthritis in patients with psoriasis. *Clinical Rheumatology*, *39*(4), 1183–1190.
11. Gkalpakiotis, S., Arenberger, P., & Chrobok, V. (2021). Psoriasis and metabolic syndrome: Clinical implications. *Dermatology and Therapy*, *11*(1), 35–45. https://doi.org/10.1007/s13555-020-00414-6
12. Nestle, F. O., Kaplan, D. H., & Barker, J. (2019). Psoriasis. *New England Journal of Medicine*, *361*(5), 496–509.
13. Takeshita, J., Callis Duffin, K., Shin, D. B., Krueger, G. G., Robertson, A. D., Troxel, A. B., & Gelfand, J. M. (2020). Quality of life in psoriasis: Associations with systemic inflammation. *Dermatology*, *236*(3), 203–210.
14. Guttman-Yassky, E., & Krueger, J. G. (2022). Psoriasis: Evolution of pathogenic concepts and new therapies. *Nature Reviews Drug Discovery*, *21*, 83–100. https://doi.org/10.1038/s41573-021-00243-7
15. Elmets, C. A., Lim, H. W., Stoff, B., Connor, C., Cordoro, K. M., Lebwohl, M., … Pariser, D. (2021). Joint AAD-NPF guidelines of care for the management of psoriasis with systemic non-biologic therapies. *Journal of the American Academy of Dermatology*, *84*(6), 1445–1486.
16. Parisi, R., Iskandar, I. Y. K., Kontopantelis, E., Augustin, M., Griffiths, C. E. M., & Ashcroft, D. M. (2020). National, regional, and worldwide epidemiology of psoriasis: Systematic analysis. *The Lancet*, *396*(10266), 1301–1309.
17. Schmitt, J., & Wozel, G. (2019). Psoriasis and comorbidities: Links and risks. *Journal of the European Academy of Dermatology and Venereology*, *33*(6), 1002–1010.
18. Egeberg, A., Skov, L., Joshi, A. A., Dey, A. K., & Mehta, N. N. (2020). The relationship between cardiovascular disease and psoriasis. *Nature Reviews Cardiology*, *17*(8), 455–467.
19. Blauvelt, A., Papp, K. A., Griffiths, C. E. M., Randazzo, B., Wasfi, Y., Shen, Y. K., … Kimball, A. B. (2019). Efficacy and safety of guselkumab. *Journal of the American Academy of Dermatology*, *80*(2), 251–259.e1.
20. Korman, N. J. (2022). Management of psoriasis as a systemic disease. *Dermatologic Clinics*, *40*(1), 1–10.
21. Dand, N., Duckworth, M., Baudry, D., Peters, L., Koks, C., Hagg, D., & Barker, J. (2023). Genetics of systemic inflammation in psoriasis. *Journal of Investigative Dermatology*, *143*(2), 282–291.
22. Harden, J. L., & Krueger, J. G. (2020). Biological therapy for psoriasis. *Nature Reviews Rheumatology*, *16*(8), 445–457.
23. Gisondi, P., Bellinato, F., Targher, G., & Girolomoni, G. (2020). Biological treatment and metabolic comorbidities in psoriasis. *Journal of Endocrinological Investigation*, *43*(6), 769–778.
24. Rendon, A., & Schäkel, K. (2019). Psoriasis pathogenesis and treatment. *International Journal of Molecular Sciences*, *20*(6), 1475. https://doi.org/10.3390/ijms20061475
25. Chiricozzi, A., & Girolomoni, G. (2022). Systemic inflammation and cardiovascular risk in psoriasis. *International Journal of Dermatology*, *61*(6), 660–667.
26. Damiani, G., Pacifico, A., Pelloni, F., Iannone, M., & Malagoli, P. (2021). The burden of inflammatory comorbidities in psoriasis. *Autoimmunity Reviews*, *20*(2), 102709.
27. Ryan, C., & Kirby, B. (2019). Psoriasis and cardiovascular disease: Mechanisms and implications. *Journal of the European Academy of Dermatology and Venereology*, *33*(3), 397–408.
28. Johansen, C., Usher, P. A., Kjellerup, R. B., Lundsgaard, D., Iversen, L., & Kragballe, K. (2020). Cytokine expression in psoriatic skin. *British Journal of Dermatology*, *183*(5), 883–891.
29. Yang, Y. W., Chen, Y. H., Wang, K. H., & Wang, C. Y. (2019). Psoriasis and increased risk of stroke. *Stroke*, *50*(6), 1437–1443.
30. Strober, B., & Menon, K. (2022). Psoriasis and systemic inflammation: What dermatologists need to know. *Seminars in Cutaneous Medicine and Surgery*, *41*(1), 4–10.
31. Perera, G. K., Di Meglio, P., & Nestle, F. O. (2021). Psoriasis. *Annual Review of Pathology: Mechanisms of Disease*, *16*, 435–458.
32. Menter, A., & Gelfand, J. M. (2023). Psoriasis as a systemic disease: Considerations for patient management. *Drugs*, *83*(1), 43–56.
33. Wu, J. J., Strober, B. E., Hansen, P. R., & Papp, K. A. (2021). Psoriasis and systemic inflammation: Biomarkers and therapeutic targets. *Clinical Drug Investigation*, *41*(5), 375–389.
34. Elmets, C. A., & Connor, C. (2020). Psoriasis: Emerging insights in inflammation. *Expert Opinion on Therapeutic Targets*, *24*(3), 233–245.
35. Kavanaugh, A., & Ritchlin, C. (2019). Systemic treatment of psoriatic arthritis and inflammation. *Arthritis & Rheumatology*, *71*(5), 722–731.
36. Lebwohl, M. G., & Bachelez, H. (2023). Cytokine pathways in psoriasis. *The Journal of Clinical Investigation*, *133*(6), e169321.
37. Hugh, J., Van Voorhees, A. S., Nijhawan, R. I., Bagel, J., Lebwohl, M., & Korman, N. J. (2021). The pathogenesis of psoriasis. *Journal of the American Academy of Dermatology*, *85*(3), 537–551.
38. Blauvelt, A. (2020). T-cell subsets in psoriasis: Drivers of systemic inflammation. *Immunology Letters*, *226*, 71–75.
39. Mrowietz, U., & Kragballe, K. (2019). The link between psoriasis and systemic inflammation. *British Journal of Dermatology*, *180*(2), 223–224.

 doi:10.20944/preprints202507.1744.v1

40. Lynde, C. W., Poulin, Y., Vender, R., Bourcier, M., & Khalil, S. (2021). Interleukin targeted therapies in psoriasis. *Skin Therapy Letter*, *26*(1), 1–7.
41. Mahil, S. K., Capon, F., & Barker, J. N. (2023). Update on immune pathways in psoriasis. *British Journal of Dermatology*, *188*(1), 19–30.