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Review Article

Prurigo as the early sign of HIV infection: a review

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ABSTRACT

Prurigo is a common dermatological condition in HIV-infected individuals, particularly those with low CD4 counts. This condition can be the first manifestation and as the early sign of HIV-infected individuals. One form of prurigo in HIV-positive patients is prurigo nodularis. It presents with intensely pruritic, hyperkeratotic papules or nodules lesions, significantly impairing quality of life. The pathogenesis of PN involves complex immune dysregulation, including Th2-mediated inflammation and the release of cytokines like IL-31, which contribute to inflammation and pruritus. HIV infection exacerbates these processes, making PN more prevalent and severe in immunocompromised individuals. Early detection of prurigo and appropriate treatment, including rapid antiretroviral therapy, can help reduce the frequency and severity of prurigo in HIV-positive patients. Current treatments include topical steroids, UV therapy and systemic medications, with novel therapies targeting specific cytokines under investigation. Dermatologists are also encouraged to screen for psychiatric comorbidities due to the profound psychosocial impact of PN. This review aims especially for health workers to remind the importance of early detection of dermatological signs of prurigo in patients at risk of HIV, as an important step in improving clinical outcomes and patient quality of life.

Keywords: Antiretroviral therapy, Cytokines, HIV, Inflammation and pruritus, Prurigo nodularis

INTRODUCTION

Prurigo is a skin condition characterized by intensely itchy papules, plaques or nodules.[1] It can be classified temporally as acute, subacute or chronic (≥6 weeks).[1,2] Chronic prurigo has been defined as a distinct disease with chronic pruritus, prolonged scratching behavior and pruriginous lesions. Clinical subtypes include popular, nodular, plaque, umbilicated and linear prurigo.[3] Prurigo is a common dermatological condition in HIV-infected individuals, particularly those with low CD4 counts.[4]

It is characterized by multiple, intensely pruritic nodular lesions resulting from chronic rubbing and scratching.[5] Prurigo can be an early marker of HIV infection, with a prevalence of 14.5% among HIV patients in one study.[4] It is more frequent in patients with CD4 counts below 50/µl. The condition is often challenging to treat, especially in immunocompromised hosts.[5] However, antiretroviral therapy can be effective in managing prurigo in HIV patients.[6] Early detection and rapid antiretroviral therapy can help reduce the frequency of prurigo in HIV-positive patients.[4] This review aims to provide an in-depth analysis of prurigo, with a particular focus on its association with HIV, including epidemiology, clinical manifestations and therapeutic strategies. By examining current evidence, we hope to highlight the challenges and potential opportunities in the management of this condition, particularly in the context of HIV infection.

REVIEW

The research design used in this study is article review method, utilizing the keywords prurigo nodularis (PN), HIV, cytokines, antiretroviral therapy (ART), inflammation and pruritus. The literature sources include

PubMed, Google Scholar and ScienceDirect. The authors then reviewed each journal that met the criteria, engaged in discussions and conducted cross-checks with other primary sources.

HIV infection causes profound immune dysregulation, primarily through depletion of CD4+ T cells. This depletion occurs most extensively in the gastrointestinal tract, particularly affecting CCR5+ CD4+ T cells. The initial massive destruction of CD4+ memory T cells is typically countered by regeneration, but this process is unstable long-term due to chronic immune activation. HIV impacts various CD4+ T cell subtypes differently, with Th17 cells being most compromised, while regulatory T cells may increase in immunosuppressive activity.[7]

The infection leads to aberrant memory cell production and T-cell repertoire deficits, compromising both CD4+ and CD8+ T-cell responses. Chronic immune activation also results in abnormal accumulation of effector T cells in lymph nodes and collagen deposition, further disrupting T cell homeostasis Understanding these complex mechanisms is crucial for developing effective immunotherapies against HIV.[7] Th2-mediated inflammation plays a crucial role in prurigo development, with cytokines like IL-4 and IL-31 being key mediators. IL-31, primarily produced by Th2 cells, is a potent pruritus-inducing cytokine involved in various inflammatory and pruritic conditions.[8] It interacts with other cytokines to create a proinflammatory environment in the skin, leading to chronic itch. The pathogenic role of Th2 cells in prurigo is supported by the effectiveness of recombinant interferon-gamma treatment, which selectively down-regulates Th2 cytokines. IL-31 acts through the IL-31RA/OSMRβ receptor complex, expressed on neurons and various skin cells, mediating inflammatory responses and stimulating itch.[9]

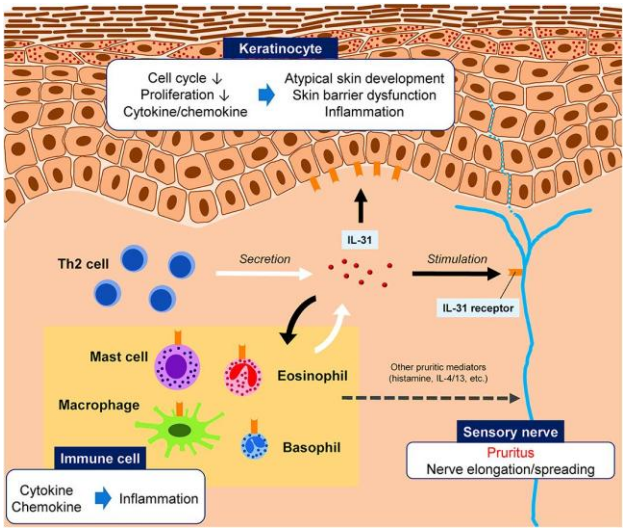

Figure 1: Keratinocyte.

The pathogenesis of prurigo involves a complex interplay between keratinocyte dysregulation, immune cell activation, inflammatory mediators, and sensory nerve alterations. Keratinocytes exhibit upregulation of the cell cycle and increased proliferation, contributing to abnormal skin development and thickened pruriginous lesions. Additionally, keratinocytes secrete cytokines and chemokines that amplify the local inflammatory response. These changes result in atypical skin development and skin barrier dysfunction, allowing increased penetration of allergens and moisture loss, further perpetuating inflammation. In the extracellular environment, T-helper 2 (TH2) cells play a pivotal role by secreting interleukin (IL)-31, a key cytokine in the pathogenesis of prurigo.

IL-31 binds to its receptor on keratinocytes and immune cells, driving inflammation and sensory activation. Immune cells such as mast cells, macrophages, basophils, and eosinophils are recruited and activated, releasing additional cytokines and inflammatory mediators. This cascade intensifies local inflammation and contributes to the chronicity of the condition. Cytokines, including histamine, IL-4, and IL-13, activate sensory nerve endings, leading to the sensation of itch. Persistent inflammation promotes the elongation and spreading of sensory nerves, exacerbating pruritus and perpetuating the itch-scratch cycle. Together, these mechanisms create a self-reinforcing loop of keratinocyte dysfunction, immune activation, and sensory nerve sensitization, driving the clinical manifestations of prurigo.[21]

This cytokine is primarily produced by T helper 2 cells, macrophages, dendritic cells and eosinophils. IL-31 signaling activates JAK/STAT, P13K/AKT and ERK/MAPK pathways, inducing inflammatory responses and stimulating itch sensations.[10] Elevated levels of IL-31 are observed in atopic dermatitis and prurigo nodularis, making it a promising target for therapeutic interventions.[10,11]

Neurological and cutaneous changes

Peripheral nerve damage can lead to sensitization of cutaneous nociceptors, contributing to neuropathic pain. Studies have shown that after nerve injury, both myelinated and unmyelinated nociceptors exhibit lower mechanical and thermal thresholds. This sensitization is characterized by increased responsiveness to stimuli, decreased activation thresholds and a higher incidence of spontaneous activity. Changes in neurotrophic factor signaling and neurochemical phenotypes of nociceptors may underlie these functional alterations. Various conditions, including trauma, metabolic disorders and genetic diseases, can cause peripheral neuropathies affecting cutaneous pain perception. Recent research has also implicated non-neuronal skin cells, such as keratinocytes, in cutaneous nociception and peripheral neuropathies, opening new avenues for potential therapeutic interventions that target peripheral mechanisms of pain.[12] Atopic dermatitis (AD) is a complex skin condition characterized by barrier dysfunction, immune abnormalities and pruritus, which

interact in a positive feedback loop.[13] Skin barrier disruption, often due to factors like filaggrin mutations, allows penetration of external antigens, triggering immune responses. This "outside-to-inside" mechanism is complemented by an "inside-to-outside" pathway, where inflammatory factors disrupt barrier homeostasis.[14] Th2 cytokines, including IL-4 and IL-13, contribute to inflammation and directly activate sensory neurons, inducing pruritus. Additionally, Th2-produced IL-31 provokes itching and decreases filaggrin expression, further compromising the skin barrier. Recent evidence suggests AD is more prevalent in adults than previously thought and may predispose individuals to other atopic diseases.[15] Understanding these interconnected mechanisms is crucial for developing new therapeutic strategies for AD.

Clinical manifestation

Prurigo nodularis (PN) in advanced HIV typically presents with symmetrical, hyperkeratotic and intensely itchy papules or nodules, significantly impairing quality of life and mental health, with over 37% of patients meeting criteria for severe depression. Black patients report higher itch intensity than White patients, highlighting disparities in symptom severity. The condition is difficult to treat, particularly in immunocompromised individuals, with current therapies including topical steroids, UV therapy and systemic treatments and novel agents targeting neurokinin-1, opioid and interleukin-31 receptors under investigation. Chronic scratching may trigger PN and dermatologists are advised to screen for psychiatric comorbidities given the condition's profound psychosocial impact.[16]

DISCUSSION

Prurigo nodularis (PN) is a chronic inflammatory skin condition characterized by intensely pruritic, hyperkeratotic nodules on the extremities and trunk.[17] Clinical evaluation of PN involves assessing risk factors, documenting scratch history and identifying characteristic lesions.[18] Diagnostic workup includes a comprehensive review of systems, considering potential systemic diseases and assessing disease severity.[19] HIV infection is a significant risk factor for PN, often presenting as an initial cutaneous manifestation. Laboratory tests, including HIV testing, are essential to confirm diagnosis and rule out secondary conditions and PN is associated with various comorbidities, including systemic diseases and mental health conditions.[17,18] As a dermatological manifestation, prurigo nodularis (PN) is commonly observed in HIV-infected individuals, particularly those with low CD4 counts.[4,20] It presents as hyperkeratotic nodules on the extremities and trunk, significantly impacting patients' quality of life. Early detection and management of HIV, including antiretroviral therapy (ART), play a crucial role in resolving PN and improving patient outcomes. Combination therapy with raltegravir, an integrase inhibitor, has shown promising results in rapidly reducing viral load and improving PN symptoms within weeks of initiation. The pathogenesis of PN in HIV patients is not fully understood but may be related to inflammatory mediators. Effective management of PN and other HIV-related dermatoses requires a multidisciplinary approach, combining topical and systemic treatments with ART.[20]

CONCLUSION

Prurigo nodularis (PN) is a common and debilitating condition in HIV-infected individuals, especially those with low CD4 counts. Its pathogenesis involves immune dysregulation and 3cytokines like IL-31, leading to chronic pruritus. Early HIV detection and antiretroviral therapy (ART) are essential for managing PN. While current treatments provide some relief, novel therapies targeting specific cytokines offer hope for improved outcomes. A multidisciplinary approach is crucial for effective management and better patient quality of life.

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