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Mechanisms Driving Altered Treatment Responses in Vulvar Dermatological Conditions with Autoimmune Components

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Abstract

Vulvar dermatological conditions, including lichen sclerosus, lichen planus, psoriasis, and eczema, often have autoimmune components influencing their pathophysiology and treatment responses. Patients with systemic autoimmune comorbidities frequently exhibit altered responses to standard therapies, suggesting a complex interplay between local and systemic immune mechanisms. This review explores the underlying immunological pathways, cytokine profiles, and genetic factors contributing to variable treatment outcomes in these conditions. By elucidating these mechanisms, we aim to inform personalized therapeutic strategies and highlight areas for future research.

Keywords: *Vulvar dermatology, autoimmune mechanisms, lichen sclerosus, lichen planus, psoriasis, cytokine signaling*

1. INTRODUCTION

Vulvar dermatologic conditions, particularly autoimmune-driven disorders such as lichen planus, lichen sclerosus, psoriasis, and eczema, can present considerable clinical challenges due to their chronic nature, relapsing course, and potential to cause severe discomfort. Given their complex etiologies and ability to impact quality of life, understanding the immunopathogenesis of these conditions is critical in the advancement of both therapeutic and diagnostic management approaches.

Evidence suggests that autoimmune mechanisms are central to these conditions' pathophysiology and treatment response, especially in patients with systemic autoimmune comorbidities (Terlou et al, 2012; Torres et al., 2022). This connection further reinforces the importance of considering autoimmune comorbidities when managing vulvar dermatoses. Lichen sclerosus, for instance, has been linked to autoantibodies targeting extracellular matrix protein 1 (ECM1), abnormal T-cell activity, and dysregulated cytokine production (Fergus et al., 2020; Terlou et al., 2012). Together, these dysregulations suggest an underlying autoimmune component. Similarly, vulvar lichen planus is thought to involve a Th1-mediated immune response involving cytotoxic T-cell-induced apoptosis of basal keratinocytes, leading to mucosal damage and chronic inflammation (Xie et al., 2023). The Th1-driven mechanisms described in lichen planus emphasize the diversity of immune responses involved in vulvar dermatoses. They demonstrate that the immune system can target skin tissue through various mechanisms, with each contributing to inflammation in a different

way. While lichen planus is primarily mediated by a Th1 response, other conditions, such as psoriasis, exemplify how alternative immune pathways can lead to chronic inflammation. This immune-mediated disorder is driven by the IL-17/IL-23 axis and TNF-a, leading to excessive keratinocyte proliferation and persistent inflammation (Campanati et al., 2021). This pathway, though separate from lichen planus, shares key features that all contribute to chronic inflammation, such as immune-regulated keratinocyte damage and cytokine activation. This further portrays the way in which cytokines and immune signaling molecules play a role in the pathology of various dermatologic conditions. In comparison, atopic dermatitis and vulvar eczema are primarily associated with a Th2-mediated immune response and also involve immune dysregulation that can contribute to therapy resistance in those with systemic autoimmune diseases (Pichardo-Geisinger, 2017; Ong 2006). Collectively, these mechanisms highlight the overlapping immune pathways involved in vulvar dermatoses and their role in disease progression.

Appreciating the relationship between vulvar dermatological conditions and autoimmunity, this review aims to explore the underlying immune mechanisms, cytokine interaction, and genetic contributions that may influence disease expression and treatment outcomes. By better understanding these factors, we seek to inform more targeted and individualized therapeutic strategies and highlight critical areas for future research.

2. METHODS

2.1 Literature Search Strategy

An extensive literature search was conducted using PubMed, Scopus, and Google Scholar to identify studies examining autoimmune mechanisms and treatment responses in vulvar dermatological conditions. The searched was conducted between February 17th, 2025, and February 28th, 2025 using the keywords: "vulvar dermatology," "autoimmune mechanisms," "treatment response," "immune pathways," "lichen sclerosus," "lichen planus," "psoriasis," and "eczema." Filters were applied to include studies published within the last 10 years (2015–2025) to ensure relevance to contemporary immunological and therapeutic advancements. We focused on studies published in peer-reviewed journals, prioritizing studies focusing on cytokine interactions, genetic markers, and clinical treatment outcomes in patients with autoimmune comorbidities.

2.2 Data Extraction and Synthesis

Studies were included if they investigated the immune mechanisms underlying vulvar dermatological conditions, assessed treatment outcomes in patients with and without systemic autoimmune diseases, or explored cytokine profiles, immune cell activity, and genetic predispositions affecting treatment responses. Only articles published in English with full-text availability were considered. A total of 90 articles were obtained. Case reports and small case series with fewer than five patients were excluded, along with studies that lacked specific data on immune pathways or treatment responses. A narrative review of the most relevant articles was provided.

3. RESULTS

3.1 Immune Mechanisms in Vulvar Dermatological Conditions

3.1.1 Vulvar Lichen Sclerosus

Lichen sclerosus (LS) is a chronic inflammatory dermatosis primarily affecting the female vulva, with an autoimmune-suspected pathogenesis involving genetic predisposition, chronic irritation, infection, and immune dysregulation (Bao et al., 2021; Fergus et al., 2020). Despite being considered a rare disease, LS is a leading cause of vulvar pruritus and structural changes (Tran et al., 2019). Its underdiagnosis and underreporting contribute to its enigmatic nature, even more than a century after its initial clinical description in 1887 (Tran et al., 2019).

3.1.2. Emerging Insights into LS Pathogenesis

Recent studies indicate that immune dysregulation plays a central role in LS pathophysiology, with elevated Th1 and Th17 cytokines, such as interferon-gamma (IFN-γ) and interleukin-17 (IL-17), contributing to chronic inflammation and fibrosis (Fergus et al., 2020; De Luca et al., 2023). Autoantibodies against extracellular matrix proteins may also influence disease severity and resistance to corticosteroid treatment.LS features local immune dysregulation, particularly involving Langerhans cells, which are critical for antigen presentation and immune activation (Bao et al., 2021). Histopathological studies reveal aberrant T-cell activity, with excessive dermal lymphocyte

infiltration and disrupted cytokine expression patterns (Bao et al., 2021; Fergus et al., 2020). Genetic studies suggest an association with HLA class II antigens, including susceptibility links to HLA-DQ7 and HLA-DR12 and protective effects from HLA-DR17 (Lewis et al., 2018). Furthermore, LS is frequently comorbid with autoimmune diseases, especially in women, who exhibit high rates of thyroid autoantibodies.

3.2. Vulvar Lichen Planus

3.2.1. Immune Responses and Mucosal Involvement

Lichen planus (LP) is a chronic inflammatory disease characterized by T-cell-mediated immune responses, particularly involving IL-2, IL-6, and TNF-α. These cytokines drive mucosal involvement through keratinocyte apoptosis and sustained inflammation.

3.3. T-Cell-Mediated Immune Responses

CD8+ cytotoxic T cells play a major role in LP pathogenesis by inducing keratinocyte apoptosis via perforin and granzyme B. Pro-inflammatory cytokines contribute to immune dysregulation:

- IL-2 – Enhances T-cell proliferation and immune activation.
- IL-6 – Promotes inflammation and angiogenesis, particularly in oral LP.
- TNF-α – Mediates keratinocyte damage and chronic inflammation.

The Th1 and Th17 pathways further exacerbate LP, with IFN-γ, IL-17, and IL-23 sustaining immune dysregulation. Altered antigen presentation due to dendritic cell and macrophage dysfunction results in prolonged T-cell activation. Genetic predisposition, involving HLA-A3, HLA-B7, and HLA-DR1, may contribute to heightened immune responses. Environmental factors, such as viral infections (HCV, HPV, EBV) and microbial dysbiosis, can also modulate disease severity and treatment response.

3.3.1. Vulvar Psoriasis

Psoriasis is primarily driven by dysregulation of the IL-23/Th17 axis, leading to excessive keratinocyte proliferation and chronic inflammation (Rendon & Schäkel, 2019). The presence of systemic autoimmune diseases, such as rheumatoid arthritis and lupus, can exacerbate treatment resistance to biologics and conventional immunosuppressants (Liang et al., 2017).

Psoriasis exhibits both autoinflammatory and autoimmune characteristics, with dendritic cells initiating disease through responses to antimicrobial peptides like LL37 (Liang et al., 2017). LL37 forms complexes with self-DNA and RNA, activating dendritic cells via Toll-like receptors, leading to IFN-α and IL-23 production (Harden et al., 2015; Liang, 2017).

Distinct psoriasis subtypes involve unique immune pathways:

- Guttate psoriasis – Involves molecular mimicry between streptococcal M proteins and keratin 17, triggering T-cell activation in HLA-Cw6-positive individuals (Johnston et al., 2017).
- Pustular psoriasis – Associated with IL-1β and IL-36 upregulation, though IL-17 remains a central player (Johnston et al., 2017; Bissonnette et al., 2017).
- Nail psoriasis and psoriatic arthritis – Involve TNF-α, IL-6, and IL-8, with IL-17 contributing to joint pathology via RANKL-mediated osteoclast activation (Wilsmann-Theis et al., 2018).

Psoriasis also features autoantigens, such as LL37 and ADAMTSL5, that stimulate autoreactive CD4+ and CD8+ T cells, exacerbating inflammation (Boutet et al., 2018; Sakkas et al., 2017). Therapies targeting TNF-α, IL-23, and IL-17 have proven effective, but alternative pathways may be involved in specific disease subtypes.

3.3.2. Atopic Dermatitis

Atopic dermatitis (AD) is a complex, multifactorial disease characterized by epidermal barrier dysfunction, immune dysregulation, and genetic susceptibility. Despite extensive research, the precise order of pathogenic events remains unclear, leading to competing "outside-in" and "inside-out" models.

The "outside-in" model suggests that primary epidermal barrier dysfunction allows allergen penetration, triggering immune activation. Conversely, the "inside-out" model proposes that immune dysregulation, particularly Th2 activation, initiates AD pathogenesis (Guttman-Yassky et al.).

3.4. Impact of Autoimmune Comorbidities

The immune mechanisms underlying vulvar dermatological conditions highlight the complexity of immune dysregulation in LS, LP,

psoriasis, and AD. Each condition involves distinct yet overlapping immune pathways, emphasizing the need for targeted therapeutic approaches. Future research into genetic predispositions, environmental triggers, and novel immunomodulatory treatments will be essential for improving disease management and patient outcomes.

Key immune factors that play a role in maintaining a host's system are CD4 T cells, specifically Th1 cells that release pro-inflammatory cytokines and immune mediators such as IL-1, IL-7, IL-15, INF-y, TNF-a, and many others (Corazza et. al., 2021). Long-standing, chronic production of pro-inflammatory cytokines and an imbalance of anti-inflammatory cytokines can predispose patients to tissue damage, and immune dysfunction, which can play a potential role in autoimmune pathogenesis. Patients with concurrent autoimmune diseases can exhibit increased resistance to corticosteroids, immunosuppressants, and biologics. This can lead to serious consequences due to LS's association with vulvar cancers (VC), and VC's ability to evade immune mechanisms leading to its aggressive behavior and poor clinical outcomes (Borella et. al., 2020). Variability in immune responses results in alterations in the immune and tumor microenvironment, creating an immune microenvironment that allows for tumor growth and evasion of host immune responses. Functioning immune systems have a fine balance of local pro- and anti-inflammatory mediators that play a role in monitoring and altering disease progression. Systemic inflammation and circulating autoantibodies in autoimmune conditions can alter the balance of these mediators resulting in the progression of disease states. Serologic testing can be done to identify circulating autoantibodies that may predispose patients to certain autoimmune conditions. In adult patients with LS, there was a significant portion of patients who had an associated concurrent autoimmune disorder. The most prominent autoimmune disorders patients with LS were diagnosed with psoriasis, Hashimoto's thyroiditis, lichen planus, vitiligo, and Grave's disease (Guttentag et.al., 2025). Many of the concomitant autoimmune conditions patients with LS are suffering from tend to be thyroid disorders which may warrant the need to screen patients who present with thyroid disorders as their first diagnosis for vulvar pathology to reduce future comorbid conditions.

Vulvar diseases such as vulvar lichen sclerosus (LS) and lichen planus (LP) are currently described as chronic inflammatory skin disorders with poorly understood etiologies. Current publications revealed that these disorders may have an autoimmune component to them. Studies have shown that patients with LS and LP are frequently diagnosed with other autoimmune disorders such as vitiligo and thyroid disease and have an associated HLA polymorphism of class II antigen DQ7 in LS and HLA DRB*0201 in LP (Terlou et al., 2012). Genetic variations in HLA haplotypes play a critical role and can potentially dictate a patient's responsiveness to specific treatments. A patient's ability to respond to certain corticosteroids, biologics, and immunosuppressants is imperative to patient morbidity due to the strong association between LS and leukoplakia of the vulva as well as vulvar cancer (Gulin et al., 2023). Variations in HLA haplotypes in LS can alter the immunologic microenvironment, resulting in overexpression of Th1 cells and inflammatory cytokines. Overexpression of pro-inflammatory cytokines and lymphocytes alters a patient's immune response making them more susceptible to succumbing to clinical effects of vulvar cancers.

4. DISCUSSION

4.1. Interpretation of Findings

The current literature strongly supports the role of autoimmune mechanisms in the pathophysiology and treatment response of vulvar dermatoses, specifically lichen sclerosus (LS), lichen planus (LP), psoriasis, and atopic dermatitis.

4.1.1. Immunological Mechanisms

All four conditions (LS, LP, psoriasis, and atopic dermatitis) clearly demonstrate T-cell mediated mechanisms at the core of their pathophysiology. Vulvar LS and LP are chronic inflammatory disorders that share similar pathogenic processes which can predispose them to malignant transformation. Histologically, both disorders are characterized by a band-like lymphocytic infiltrate, epidermal thinning, and vacuolar changes in the basal epidermal layer (Terlou, 2012). In LS, proinflammatory Th1-type cytokines and immune-mediators, such as IL-1, IL-7, IL-15, IFN-γ, TNF-α, IL-2 receptor (CD25), caspase 1, and ICAM-1, are significantly up-regulated, alongside elevated tissue expression of chemokine receptors CXCR3 and CCR5 (Terlou, 2012). LP is

associated with an increase in CD4+ T cells, CD8+ T cells, and CD19+ B cells, as well as IL-2, IL-6, and TNF-α (Terlou, 2012).

An interesting shared finding between LS and LP is the increased regulatory T-cell (Treg) count. Under typical conditions, Treg cells control unwanted immune responses through their immunosuppressive function which are known to have a critical role in maintaining immune tolerance. However, LP and LS concurrently showed an overexpression of microRNA-155 (miR-155), which may inhibit Treg cell activity (Terlou, 2012). This reduced Treg function leads to both impaired immune tolerance toward self-antigens and autoimmunity. Chronic inflammation also induces tissue damage and the generation of reactive oxygen species (ROS), further contributing to the formation of autoantibodies found in both diseases. Overall, these immunological markers involved in abnormal immune control foster a pathway to autoimmunity in both LS and LP. These markers can be used as potential therapeutic targets, but warrant further study and analysis for therapeutic applications. Minimal literature exists on how the components of the immune response of these diseases impact treatment. One study found that increased CD4+ T lymphocyte infiltration is associated with a better LP response to therapy (Vicic, 2023). Identifying which patients respond best to specific therapies is crucial for optimizing treatment outcomes, improving patient care, and maximizing resource allocation.

4.1.2. Genetics

LS and LP have been found to have an association with HLA class II antigens. One application of uncovering the genetic background of these diagnoses is determining a patient's responsiveness to specific treatments and disease progression. For example, familial lichen planus is characterized by early onset and development of atypical forms with mucosal involvement, often with a more severe and refractory course when compared with nonfamilial cases (Brănișteanu, 2016). Once again, identifying predictive factors can help physicians create more personalized treatment plans.

4.1.3. Comorbidities

The literature demonstrates a strong association of LS with other autoimmune comorbidities, including vitiligo, thyroiditis, type 1 diabetes, or alopecia areata, with rates ranging between 14–34% in women (Torres, 2022). Such findings have important applications for selecting treatments for this population of patients. This is because patients with autoimmune diseases may have increased resistance to corticosteroids, immunosuppressants, and biologics due to the significant loss of excreting cells and the low regenerative capacity of the target tissues (Elkoshi, 2024). This shows the need to create more effective therapies for these patients, as autoimmune components driving these vulvar dermatological conditions can alter treatment response.

4.1.4. Treatments

Current first-line treatments for these disorders are the local application of topical steroids, with the goal of alleviating clinical symptoms and preventing complications, however, they do not offer a cure (Chamli, 2023 and Arnold, 2024). Moreover, recent studies of vulvar LS indicate that even after treatment, a substantial rate of patients may still have residual disease (Corazza, 2021). This illustrates the importance of new treatment strategies, potentially those that target the underlying autoimmune components of these conditions. Promising treatment modalities targeting immunological components of these disorders include photodynamic therapy and Janus kinase inhibitors. The possible anti-inflammatory effect of photodynamic therapy may be attributed to the reduction of TGF-β1 and/or the increase of IL-10 following treatment (Byun, 2011). Janus kinase inhibitors, such as baricitinib can block the immune cascade (Corazza, 2021).

4.2. Clinical Implications

A deeper understanding of these autoimmune mechanisms has the potential to refine clinical management strategies for vulvar dermatological conditions (Sand & Thomsen, 2018). The heterogeneity in immune responses suggests that treatment may be personalized based on biomarker profiling and immune signatures (Wang et al., 2022). For instance, assessing cytokine profiles or specific immune cell infiltrates may help predict treatment responsiveness, guiding clinicians toward more targeted interventions. Moreover, combination therapies addressing both local and systemic immune dysregulation—such as pairing topical corticosteroids with systemic immunomodulators—may offer improved

outcomes for patients with refractory disease (Corazza et al., 2021). The integration of precision medicine, leveraging advancements in immunophenotyping and molecular diagnostics, could lead to more effective and sustainable therapeutic strategies.

4.3. Limitations

Despite the insights gained from current research, several limitations must be acknowledged. The heterogeneity of study populations, variations in treatment protocols, and differing disease severities contribute to inconsistencies in reported treatment responses. Additionally, many existing studies lack longitudinal follow-up, making it difficult to establish causality between autoimmune mechanisms and treatment resistance. Future investigations can aim to standardize patient selection criteria and employ long-term observational studies to better delineate disease trajectories and therapeutic efficacy over time.

4.4. Future Directions

Further research can focus on identifying predictive biomarkers for treatment response, which could facilitate more individualized therapeutic approaches. The development and clinical evaluation of novel immunomodulatory agents, such as JAK inhibitors and precision-targeted biologics, hold promise in addressing refractory cases. Additionally, longitudinal studies investigating the evolution of autoimmune-mediated vulvar conditions and their response to emerging therapies will be crucial in optimizing patient outcomes. Moving forward, a multimodal approach integrating dermatology, immunology, and molecular medicine will be essential in advancing our understanding of these conditions and improving patient care.

This review highlights the need for further investigation of biomarkers in assessing disease presentation, progression, and treatment response. Identification of genes or proteins that may serve as biomarkers via serologic testing may introduce the ability to screen patients, recognize disease earlier, and identify specific targets for therapy.

5. CONCLUSION

In conclusion, this comprehensive review of the mechanisms driving altered treatment responses in vulvar dermatological conditions with autoimmune components highlights the complex relationship between immune dysregulation and therapeutic efficacy. The insights collected from this investigation of conditions such as lichen sclerosus, lichen planus, psoriasis and eczema reinforced the notion that all of these diseases are not just skin disorders but also represent manifestations of systemic immune aberrations often compounded by concurrent autoimmunity.

The evidence presented outlines a shared pathophysiological framework of these conditions characterized by disproportionate T-cell responses, particularly the Th1 and Th2 pathways and the involvement of various cytokines. For instance, the Th1-mediated immune response in lichen planus illustrated by the activation of CD8+ cytotoxic T cells and cytokines such as TNF-alpha and IL-6, reveals a tendency for increased inflammation and keratinocyte apoptosis, leading to treatment resistance. In the case of Lichen sclerosus, the presence of autoantibodies against ECM1 and an imbalance in pro-inflammatory cytokines exemplifies how autoimmune dynamics can exacerbate symptoms and reduce the effectiveness of first-line therapies such as high potency corticosteroids.

The role of the IL-23/Th17 axis in psoriasis further illustrates the complexity of immune interactions, where excessive keratinocyte proliferation due to dysregulated pathways can lead to a resistance to both conventional systemic treatments and biologics. Meanwhile, atopic dermatitis exhibits a contrasting Th2 dominance, where underlying genetic factors trigger severe responses that complicate the autoimmune pathologies.

The high prevalence of autoimmune comorbidities in patients suffering from these dermatoses raises considerations for their management. As highlighted, the concurrent presence of autoimmune disorders like hashimoto’s thyroiditis and vitiligo can significantly hinder treatment efficacy due to altered immune responsiveness. Corticosteroids and other immunosuppressants may provide inadequate relief due to the systemic nature of inflammation requiring alternative therapeutic strategies that are specifically tailored to individual patients and their specific immune profiles.

These discoveries call for a shift in clinical practice towards personalized medicine, emphasizing the necessity of identifying specific biomarkers that can predict treatment responses.

The potential of genetic markers, particularly in relation to HLA polymorphism, can guide dermatologists in selecting the appropriate therapies that align with the patient's unique immunological landscape. Moreover, integrating precision-targeted biologics and emerging therapies such as JAK inhibitors, can lead to significant advancements in the treatment of patients who are non-responsive to traditional treatment modalities.

Despite the significant advancements in understanding these diseases, the literature still remains hindered by a lack of longitudinal studies and homogenous treatment protocols. Future research aimed towards delineating the relationships between immune dysregulation and treatment resistance along with the identification and validation of predictive biomarkers are essential next steps in the process.

In summary, our investigation emphasizes the importance of considering both local and systemic immune responses in the management of vulvar dermatological conditions. By fostering a deeper understanding of the underlying autoimmune mechanism, we can begin to improve individualized therapies and ultimately enhance patient quality of life. The future of vulvar dermatology involves incorporating immunology, genetics and personalized medicine to develop tailored and efficacious therapeutic treatment modalities.

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