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SNEDDON- WILKINSON DISEASE: CLINICAL FEATURES, PATHOGENESIS, AND EVOLVING THERAPIES

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ABSTRACT Sneddon-Wilkinson Disease (SWD), also known as subcorneal pustular dermatosis, is a rare neutrophilic dermatosis whose pathogenesis involves a dysregulated inflammatory cascade. This narrative review provides a comprehensive overview of the disease, from its characteristic clinical and histopathological features to its complex pathogenesis, including the crucial role of the IL-36 cytokine family. We also examine the therapeutic landscape, highlighting the efficacy of first-line agents like dapsone, the utility of second-line therapies, and the promise of emerging biologic treatments. The review underscores the importance of a multidisciplinary diagnostic approach to identify associated systemic comorbidities and guides clinicians toward a more personalized management strategy.

KEYWORDS : Dermatosis, Pustular; Sneddon-Wilkinson Disease; Neutrophils.

INTRODUCTION

Sneddon-Wilkinson Disease (SWD), also known as subcorneal pustular dermatosis, is a rare chronic neutrophilic dermatosis characterized by recurrent crops of sterile, flaccid pustules primarily on the trunk and intertriginous areas. Although its precise etiology remains elusive, the disease is believed to be an autoinflammatory process driven by innate immune system activation (1). SWD can present as a solitary entity or, more frequently, in association with a wide range of hematologic, autoimmune, and neoplastic conditions. Recent evidence has highlighted the crucial role of the IL-36 cytokine family in the pathogenesis of neutrophilic dermatoses, including SWD, paving the way for targeted therapeutic strategies (2). This narrative review aims to provide a comprehensive overview of Sneddon-Wilkinson Disease, encompassing its clinical features, evolving understanding of its pathogenesis, and current and emerging therapeutic approaches, with the goal of improving the diagnosis and management of this challenging dermatological condition.

METHODS

This narrative review was conducted through a comprehensive search of the existing literature to provide a broad overview of Sneddon-Wilkinson Disease. A non-systematic search was performed using four major electronic databases: PubMed, Scopus, Web of Science, and Embase. The search strategy employed a combination of keywords, including "Sneddon-Wilkinson Disease," "subcorneal pustular dermatosis," "pathogenesis," "clinical features," "therapies," and "treatment." Articles published in English that discussed the clinical presentation, etiology, and management of the condition were included. The search was not restricted by publication date to ensure a historical perspective of the disease. A total of 15 references were ultimately selected and included in this review to synthesize the current understanding of the disease.

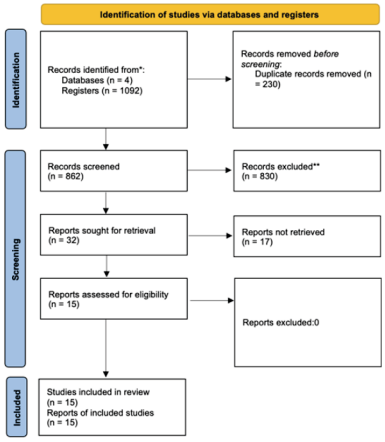

Figure. PRISMA.

Clinical Features and Diagnosis

The accurate diagnosis of Sneddon-Wilkinson Disease (SWD) is based on a careful evaluation of its distinctive clinical and histopathological features. The hallmark of SWD is the sudden onset of recurrent crops of sterile, flaccid pustules that often coalesce to form characteristic annular or serpiginous patterns. These lesions are typically found in flexural areas, such as the axillae and groin, as well as on the trunk and limbs (3). The pustules, sometimes described as a "string of pearls," are easily ruptured, leaving behind thin, crusty erosions that heal without scarring. While this presentation is most common, some patients may exhibit atypical features, including palmoplantar involvement or a more generalized distribution (4).

Histopathological examination of a skin biopsy is essential for confirming the diagnosis and ruling out mimickers. The classic finding is a large subcorneal pustule containing numerous neutrophils, with no evidence of acantholysis or significant spongiosis. The underlying dermis often shows a sparse perivascular infiltrate of lymphocytes and neutrophils. Crucially, direct immunofluorescence (DIF) studies are typically negative, which helps to differentiate SWD from other bullous diseases like IgA pemphigus and pemphigus foliaceus. This is a key diagnostic step, as it prevents misclassification and guides appropriate therapeutic management (5).

The differential diagnosis is extensive and includes conditions such as pustular psoriasis, impetigo, and acute generalized exanthematous pustulosis (AGEP). Distinguishing SWD from these entities requires a combination of clinical context, histopathological findings (e.g., the presence of Munro microabscesses in psoriasis), and microbiological cultures to rule out infection. A comprehensive diagnostic approach is essential for accurate identification and effective treatment initiation.

Pathogenesis

The pathogenesis of Sneddon-Wilkinson Disease (SWD) is complex and not yet fully understood, but it is widely considered a prototype autoinflammatory neutrophilic disorder. The disease is characterized by a massive influx of neutrophils into the subcorneal layer of the epidermis, a process mediated by a complex and dysregulated cytokine cascade. A central player in this process is the interleukin-36 (IL-36) cytokine family. IL-36 is released by keratinocytes in response to inflammatory stimuli, which in turn acts in an autocrine and paracrine manner to promote the release of additional inflammatory chemokines, such as CXCL1, CXCL2, and CXCL8. These chemokines are potent attractants for neutrophils, creating a vicious cycle of inflammation that drives the formation of the characteristic sterile pustules (6).

This deeper understanding of the IL-36 pathway has opened new avenues for targeted therapeutic strategies.

SWD is also well-known for its strong association with various systemic comorbidities, a connection that is crucial for a holistic diagnostic and therapeutic approach. A significant proportion of patients, particularly older individuals, have an underlying hematological disorder, most commonly an IgA monoclonal gammopathy (7). Other associated hematological conditions include multiple myeloma, Waldenström macroglobulinemia, and various types of lymphoma. This strong link suggests that SWD may be a cutaneous marker for an underlying hematologic dyscrasia. Furthermore, SWD has been linked to several autoimmune diseases, such as rheumatoid arthritis, Crohn's disease, and celiac disease, as well as certain solid tumors (8). This suggests that SWD may represent a paraneoplastic or para-autoimmune syndrome, where the skin pathology is a direct cutaneous manifestation of a deeper systemic process.

While the majority of SWD cases are sporadic, there are rare reports of familial clustering, suggesting that genetic factors may play a role in a minority of instances. However, no single causative gene has been identified, and the inheritance pattern is not clear. Environmental triggers, such as infections (e.g., Staphylococcus aureus) or certain medications (e.g., calcium channel blockers), have been postulated to initiate the inflammatory cascade in genetically predisposed individuals, but these remain largely speculative and anecdotal. The current consensus is that SWD is a multifactorial disease resulting from the interaction between innate immunity dysregulation and an underlying systemic condition, highlighting the need for a comprehensive diagnostic workup beyond the skin (9).

Therapeutic Approaches

The management of Sneddon-Wilkinson Disease (SWD) is primarily focused on controlling the neutrophilic inflammatory cascade and managing symptoms. Dapsone, a sulfone drug, remains the cornerstone of first-line therapy due to its potent anti-inflammatory effects, particularly its ability to inhibit neutrophil chemotaxis. Doses typically range from 50 to 200 mg daily, with a favorable response often observed within a few days to weeks (10). Close monitoring for potential side effects, such as methemoglobinemia and hemolytic anemia, is essential, particularly in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Despite its efficacy, a significant number of patients may be intolerant to dapsone or develop refractory disease, necessitating alternative treatment strategies.

When dapsone is ineffective or not tolerated, several second-line therapies are considered. Systemic corticosteroids, such as prednisone, can induce a rapid clinical response but are often reserved for short-term use in acute flares due to their long-term side effects. Retinoids, including acitretin and isotretinoin, have shown efficacy in some cases, likely by modulating keratinocyte differentiation and inflammatory responses (11). These agents, however, are associated with a range of side effects and are contraindicated in pregnancy. Immunosuppressive agents like cyclosporine, mycophenolate mofetil, and methotrexate have also been used in challenging cases with variable success, offering a systemic approach to control the underlying immune dysregulation (12). The choice of a second-line agent is often guided by the patient's individual comorbidities and tolerability profile.

The growing understanding of SWD's pathogenesis has paved the way for the development of targeted biologic therapies. As the IL-36 pathway is a key driver of neutrophilic inflammation, inhibitors of this pathway, such as guselkumab (an anti-IL-23 antibody, which indirectly blocks IL-36) and anti-IL-36 receptor antibodies (e.g., spesolimab), have emerged as promising therapeutic options, particularly for cases with significant IL-36 dysregulation (13). Clinical trials and case reports are beginning to show encouraging results with these agents in refractory neutrophilic dermatoses, including SWD. Additionally, adalimumab and etanercept, TNF-α inhibitors, have demonstrated some benefit in patients with associated inflammatory conditions like pustular psoriasis, although their efficacy in isolated SWD is less consistent (14). Other biologics targeting IL-17 (secukinumab, ixekizumab) are also being explored.

Managing refractory cases of SWD, which fail to respond to standard and second-line therapies, presents a significant clinical challenge. In these situations, a multidisciplinary approach is crucial, involving dermatologists, rheumatologists, and oncologists, especially when an underlying hematological or autoimmune disorder is suspected. Treatment may involve a combination of therapies or off-label use of biologics based on the specific inflammatory pathways identified. Additionally, therapies like colchicine and narrowband ultraviolet B (NBUVB) phototherapy have been reported to be effective in anecdotal cases (15). The future of SWD management lies in a personalized medicine approach, using genetic and molecular markers to guide the selection of the most effective and targeted therapy for each patient.

CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, Sneddon-Wilkinson Disease is a rare but distinct neutrophilic dermatosis whose pathogenesis is increasingly understood as an autoinflammatory process driven by cytokines, particularly the IL-36 family. This review highlights the importance of recognizing its characteristic clinical features, confirming the diagnosis with histopathology, and performing a systemic workup to identify frequently associated hematological and autoimmune conditions. The therapeutic landscape for SWD is evolving, moving from traditional agents like dapsone to more targeted biologic therapies that offer new hope for patients with refractory disease.

Despite these advances, significant knowledge gaps remain. The precise triggers initiating the inflammatory cascade are often unknown, and the specific molecular link between SWD and its various comorbidities requires further investigation. There is a pressing need for large-scale, randomized controlled trials to establish standardized treatment protocols and assess the long-term efficacy and safety of newer biologics. The clinical impact of this review is to equip clinicians with an updated synthesis of SWD, fostering earlier diagnosis and a more comprehensive management strategy. Future research should focus on identifying predictive biomarkers for treatment response and clarifying the genetic predispositions of this challenging condition.

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