Pruritus in Cutaneous T-Cell Lymphoma and Its Management

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KEYWORDS

• Cutaneous T-cell lymphoma • Interleukins • Pruritus • Substance P • Antidepressants
• Histone deacetylase inhibitors • Aprepitant • Visual analog scale

KEY POINTS

- In cutaneous T-cell lymphoma (CTCL), pruritus is experienced in approximately 62% to 88% of patients and is more common in late-stage mycosis fungoides, Sézary syndrome, and folliculotropic mycosis fungoides.
- The pathogenesis of CTCL-related pruritus is not completely understood; however, it seems that malignant T-cell clones, along with their accompanying dermal infiltrate, play an important role in CTCL-related pruritus.
- Different mediators of pruritus have been described in CTCL patients, including interleukin-31, nerve growth factor, and substance P.
- Worsening pruritus is associated with disease progression, relapse, or superinfection of CTCL patients. Repeated clinical pruritus assessments are warranted to assess disease status.
- Management of pruritus in CTCL patients should include effective disease therapy, neurotropic medication, proper skin care, and psychological support.

INTRODUCTION

Pruritus of lymphoma is commonly associated with both Hodgkin lymphoma (HL) and cutaneous T-cell lymphoma (CTCL) and may precede any other symptoms.[1] The prevalence of chronic itch in HL has been reported in up to 30% of patients and its specific pathogenesis is not well known. Currently, management includes supportive care along with disease therapy.[2] In CTCL, pruritus is experienced in approximately 62% to 88% of patients and is more common in late-stage mycosis fungoides (MF), Sézary syndrome (SS), and folliculotropic MF (FMF), a variant of MF distinguished by infiltration of pilosebaceous units.[3–8] In recent years, new mechanisms of pruritus in CTCL have been discovered and new therapies have been developed.[6,9,10] Because of the impact this

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symptom has on patient quality of life (QOL), this article focuses on the pathogenesis, management, and treatment of CTCL-associated pruritus.

PATHOPHYSIOLOGY IN CUTANEOUS T-CELL LYMPHOMA PRURITUS

The pathophysiology of CTCL-related pruritus has recently made remarkable advances, yet is not completely understood. Pruritus is a complex symptom that includes pruriceptive, neuropathic, neurogenic, and psychogenic causes that originate from different pathways.[11] Pruriceptive pruritus originates from stimulation of sensory nerve terminals with the cell body located in the dorsal root ganglia; thereafter the stimulus is sent to the brain through the spinothalamic cord. The identification of the mediators that participate in the stimulation of sensory nerve terminals has become an active research area for potential therapeutics. That standard treatments for pruritus are frequently ineffective for CTCL patients suggests a distinct mechanism for pruritogenesis arising from the unique cytokine profile generated by the malignant T-cell clones and tumor microenvironment.

The overall T-cell infiltrate in early MF shows a T helper (Th)1 cytokine profile (interleukin [IL]-2, IL-12, and interferon-γ), whereas in advanced MF and SS the predominant cytokine profile is Th2 (IL-4, IL-5, IL-10, and IL-13).[12] The latter cytokine profile is also observed in atopic dermatitis, and promotes immune responses mediated by eosinophils, mast cells, and immunoglobulin (Ig)E isotype.[13] Malignant T cells are also accompanied by a large number of nonmalignant immune cells, which include CD8+ tumor-infiltrating T cells, T cells with regulatory profile, dendritic cells, macrophages, and mast cells. Macrophages and mast cells have shown an important protumorigenic role.[12,14]

Among the different mediators involved in CTCL-related pruritus, interleukins play an important role. IL-2 is produced by activated T cells and promotes proliferation and differentiation of T-cell clones. Intradermal injection of IL-2 causes itchiness and erythema in healthy volunteers.[15] In addition, cyclosporine A is known to block IL-2 production, as well as the release of histamine from mast cells. This may explain the successful use of cyclosporine A in a patient with refractory SS and severe pruritus, which disappeared 2 days after treatment initiation.[16] However, because cyclosporine A causes immunosuppression, it should be avoided in CTCL patients owing to the high risk of disease progression.[17]

As mentioned previously, a predominant Th2 profile is observed in advanced disease and SS causes increased levels of IL-4, which is also observed in atopic dermatitis. The pathogenic role of IL-4 in CTCL-related pruritus or in CTCL by itself is unknown. Drugs targeting IL-4 have been developed specifically for atopic dermatitis patients; however, data in CTCL patients are not available yet.[18] IgE production is enhanced by IL-4 and increased IgE levels have been reported in CTCL patients. IgE binds to Fc receptors of mast cells, basophils, eosinophils, monocytes, and macrophages, releasing mediators such as histamine and serotonin, among others. The involvement of these mediators in pruritogenesis is well known.

Another interleukin found within a rich Th2-environment is IL-31, which is released by the Th2 cells but also by dendritic cells, mast cells, and keratinocytes. Receptors for IL-31, such as oncotic M receptor beta and receptor alpha, have been described in keratinocytes, as well as in the dorsal root ganglia.[19] Binding to its receptors induces Janus kinase and then activates signal transducers and activators of transcription, mitogen-activated protein kinase and phosphatidylinositol 3-kinase pathways.[20] Increased serum levels of IL-31 have been described in pruritic dermatitis, including atopic dermatitis, prurigo nodularis, and allergic contact dermatitis, as well as in *Staphylococcus aureus* infection.[19,21–26]

IL-31 can be expressed by circulating malignant T-cell clones.[27] Controversial results have been observed regarding serum levels of IL-31 in patients with CTCL and pruritus. Although increased serum levels of IL-31 are higher in patients with advanced disease and severe pruritus, this correlation is not clearly observed in early-stage disease with or without pruritus.[19,20] The latter might be explained by the predominant Th1 cytokine profile and that there are undetectable T-cell clones observed in blood of early-stage MF. Finally, current therapies known to induce pruritus relief, such as mogamulizumab (anti-CCR4 conjugated humanized monoclonal antibody) and histone deacetylase (HDAC) inhibitors, demonstrated decreased circulating lymphocyte IL-31 expression.[28]

Skin biopsies of CTCL samples show an increased expression of IL-31 in the epidermis and in the interstitial lymphocytic infiltrate. Moreover, increased expression of its receptors has been observed, mostly in the epidermis, including in early lesions. The increased expression was associated with significantly higher clinical pruritus scores, yet no differences were observed with regard to disease stage.[19]

Chemoattractant cytokines (with C-C motif) or chemokines are involved in CTCL-related pruritus, including CCL1 (C-C motif ligand 1) and CCL26.