Psoriasis in the Patient With Human Immunodeficiency Virus, Part 1: Review of Pathogenesis

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GOAL

To understand psoriasis in patients with human immunodeficiency virus (HIV) infection to better manage patients with these conditions

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Discuss the pathogenesis of HIV-associated psoriasis.
2. Explain the role of CD4 and CD8 T lymphocytes.
3. Describe how cytokines affect progression of HIV infection.

CME Test on page 136.

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Psoriasis is a chronic, immune-mediated skin disease affecting approximately 1% to 3% of the human immunodeficiency virus (HIV)–infected population. The presentation of psoriasis in patients with HIV varies. It either presents as the first clinical manifestation of HIV or, less commonly, appears in the advanced stages of HIV when it has progressed to AIDS.

This 2-part series reviews the pathogenesis of HIV-associated psoriasis as well as the various therapeutic regimens that have effectively treated psoriasis in patients with HIV. These therapies address the profound immune dysregulation that defines psoriasis. The first part of the series focuses on the pathogenesis of HIV-associated psoriasis.

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Psoriasis is a chronic, immune-mediated skin disease affecting approximately 1% to 3% of the human immunodeficiency virus (HIV)–infected population, an incidence equal to the general population.[1] The presentation of psoriasis in patients with HIV varies. Psoriasis may present as the first clinical manifestation of HIV or, less commonly, may appear in the advanced stages of HIV when it has progressed to AIDS.[2-4] A substantial proportion of patients with HIV-associated psoriasis have a pattern of acral involvement, often with pustules and sometimes with severe destructive nail changes.[1] Patients with AIDS and a severe exacerbation of psoriasis are more prone to developing systemic infections, such as a superinfection of *Staphylococcus aureus*, whereas systemic infections are uncommon in the immunocompetent psoriatic patient.[5,6] In patients with preexisting psoriasis, the severity of the condition is closely correlated with the progression of HIV and correspondingly low CD4 lymphocyte counts, making the prognosis of the patient with HIV-associated psoriasis overwhelmingly poor.[4,7,8]

The pathogenesis of psoriasis in patients with HIV is considered a medical paradox that revolves around 3 main quandaries. First, this T-cell–mediated disease manages to flourish in an environment of decreasing T-cell counts.[9] Second, although various therapies targeting T lymphocytes are effective in psoriasis, the condition worsens with decreasing CD4 T-cell counts in patients with HIV.[10,11] Third, HIV is characterized by a strong helper T cells type 2 (T_H2) cytokine profile and psoriasis is characterized by a strong helper T cells type 1 (T_H1) secretion pattern.[12-15]

This 2-part series discusses these quandaries as well as the various therapeutic regimens that have effectively treated psoriasis in patients with HIV by addressing the profound immune dysregulation that defines psoriasis.

Pathogenesis of HIV-Associated Psoriasis

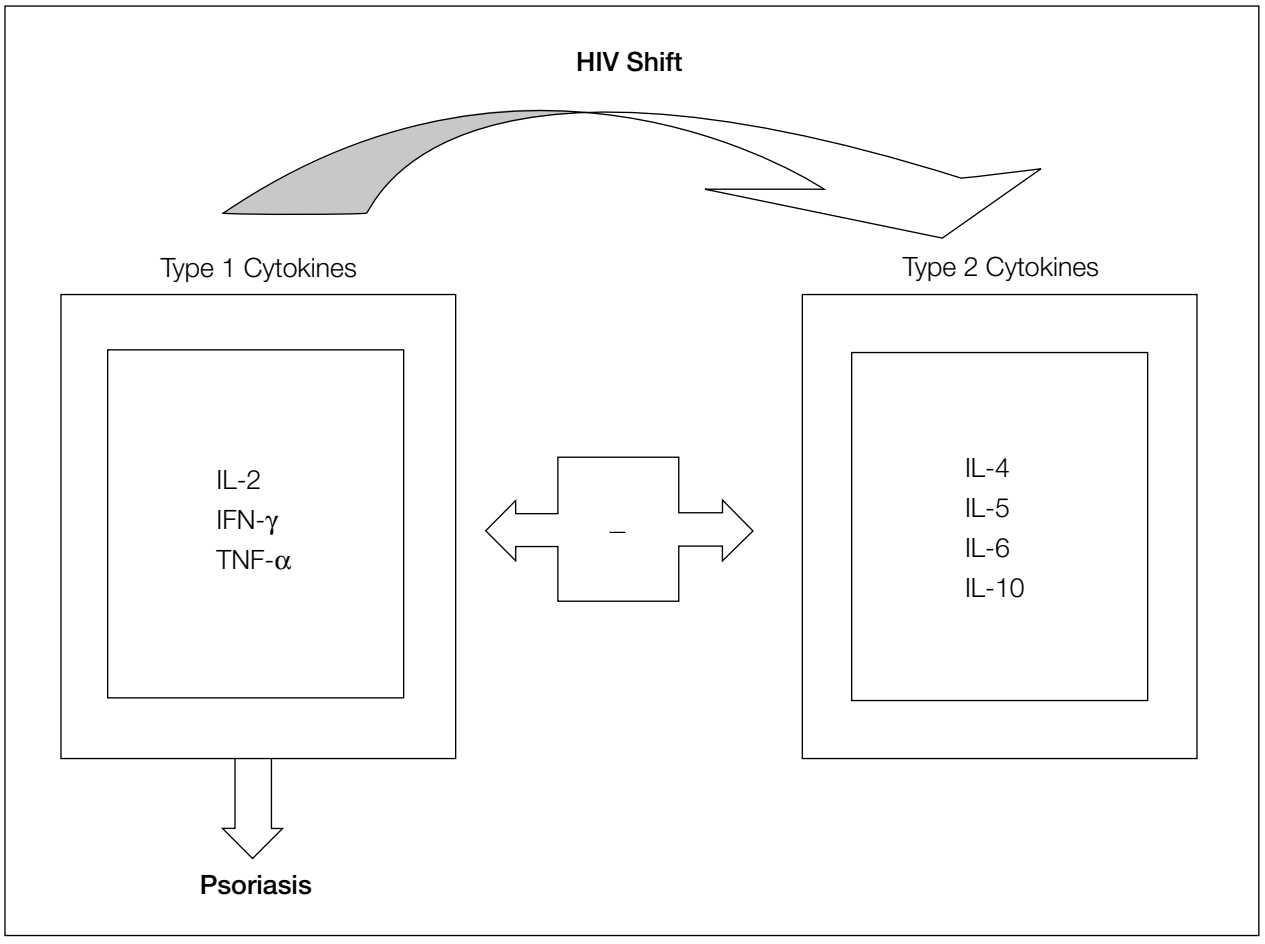
Although the etiology of HIV-associated psoriasis has yet to be clearly identified, it is postulated that both genetics and environmental factors play dynamic roles in its pathogenesis.[16] Mallon et al[17] provided the first evidence of a possible immunogenetic association between psoriasis and its expression in patients with HIV. The study compared the genomic DNA isolated from the lymphocytes of 14 men with HIV and psoriasis versus lymphocytic DNA extracted from a control group of HIV-1 seropositive men without psoriasis (n=147). The HLA-Cw6 antigen (HLA-Cw*0602 allele) was detected in 79% (11/14) of the HIV-1–positive psoriatics, while the allele, which codes for proteins capable of presenting antigens to lymphocytes, was present in only 24.5% (36/147) of HIV-1–positive controls (95% CI, 2.73–65.36; P=.0001).[17]

While there is a possibility that the association of psoriasis with the HLA-Cw*0602 allele is due to linkage disequilibrium with other recognized psoriasis susceptibility genes, it also can be inferred that the allele may be directly involved in the pathogenesis of the disease. Genetic evaluation has shown evidence for the linkage of psoriasis to the HLA-C locus and indicates that one or more genes located within this major histocompatiblity complex (MHC) may represent the key determinant of the genetic basis of psoriasis.[18]

The functional role of HLA-C is less well-defined than other HLA class I antigens. However, the identification of T-lymphocyte epitopes that are presented by certain HLA-C alleles supports the theory that HLA-C molecules are capable of presenting viral proteins such as the Epstein-Barr virus antigen and, more pertinently, HIV-1 proteins to cytotoxic CD8 T lymphocytes.[19-21] The recognition of HIV-1 proteins and subsequent activation of T lymphocytes could trigger or maintain psoriatic lesions, as this locus has been proven to play an important role in susceptibility by increasing relative risk of developing psoriasis by 14 to 24 times.[22]

While there is consensus that T cells are integral in the pathogenesis of psoriasis, it is still debatable which cells mediate the disease, either CD4 helper T cells or CD8 cytotoxic T cells. Evaluation of these various cell types has shown that there is a substantial disruption in their balance in the HIV infection.[9] Historically, it was believed that CD4 T cells were responsible for creating the immune process that characterized psoriasis and CD8 T cells were designated as having a suppressive role.[13] However, recent studies have established CD8 lymphocytes as having a more independent role in the pathogenesis of the disease. Genetically, the strong association of psoriasis with class I MHC antigens, such as the aforementioned HLA-Cw*0602, which interact exclusively with CD8 T cells, bolsters the importance of this particular cell in creating psoriatic lesions.[17,22,23] Histologically, various studies have shown that CD8 T cells, especially the memory T-cell subset, increased in concentration in the epidermis and papillary dermis of plaques as compared to uninvolved skin.[24-28] Additionally, CD8 T cells have been shown to express proinflammatory cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor α (TNF-α) more frequently than the CD4 subpopulation, which further defends the significance of this particular cell type in the pathogenesis of psoriasis.[13,15]

Recent theories on the effects of the HIV virus on T-cell populations have begun to explain



Cytokine profiles that characterize human immunodeficiency virus (HIV) infection and psoriasis. Type 1 and type 2 cytokines are mutually antagonistic, with type 1 cytokines inhibiting the release of type 2 cytokines, and vice versa. The psoriatic phenotype is promoted by type 1 cytokines, whereas HIV infection is classically thought to promote a type 1 to type 2 cytokine shift.

how an imbalance in the CD4:CD8 ratio can be responsible for the immune dysregulation of HIV-associated psoriasis. The majority of studies have shown that the virus preferentially infects memory CD4 T cells and naive CD8 T cells.[29-35] As HIV progresses and naive CD8 T cells become depleted, there is a disproportional relative expansion of the CD8 memory T-cell population that comprises more than 85% of the total CD8 T-cell count in patients with HIV versus 50% in healthy controls.[32] The overall decrease in naive CD8 T cells not only diminishes the ability of patients to fight off new infections but also allows autoimmune diseases such as psoriasis to become established.[9]

The disproportional expansion of memory CD8 T cells also explains the unique cytokine profile that permits psoriasis to present in patients with HIV. A key feature of these cytokine profiles is that they are mutually antagonistic, with T_H1 cytokines inhibiting the release of T_H2 cytokines, and vice versa.[36,37] Psoriatic lesions are associated with a T_H1 cytokine pattern (ie, high levels of IL-2, IFN-γ, and TNF-α) without a substantial component of T_H2 cytokines (ie, IL-2, IL-5, and IL-10).[13,14,26,38,39] Evidence suggests that IFN-γ is the key contributor to the hyperproliferation of psoriasis.[14,40-42] In patients with HIV without psoriasis, the cytokine profile is characterized by a strong propensity of T_H2 cytokines, especially IL-4 to IL-6 and IL-10, with a decreased production of T_H1 cytokines as the HIV infection progresses.[42,43] This shift from a T_H1 profile to a T_H2 profile has been correlated with overall prognosis, as the cell-mediated immunity of the T_H1 response permits lower rates of seroconversion and progression to AIDS. However, the cytokine pattern found in psoriatic patients with HIV is not characterized by a clean shift in cytokines to a complete T_H2 profile. Instead, due to the increased subpopulation of memory T cells, there is a distinctive increase in the production of IFN-γ, the cytokine most responsible for creating and maintaining psoriatic phenotype (Figure).[30,44-47]

The link between IFN-γ and psoriatic HIV is further supported by the unique expression of the

class II MHC antigen HLA-DR during inflammatory dermatoses such as psoriasis. While normally limited in expression to Langerhans cells and acrosyringial epithelium, HLA-DR is synthesized by keratinocytes in actively inflamed psoriatic lesions when exposed to IFN-γ, promoting further accumulation of leukocytes.[48-53] The overexpression of HLA-DR in keratinocytes has been postulated to allow for the increased frequency of exacerbations associated with bacterial infection. The ability of streptococcal pyrogenic exotoxins and staphylococcal enterotoxins to act as superantigens that stimulate production of TNF-α by HLA-DR keratinocytes permits the vicious inflammatory cycle of psoriasis in patients with HIV to continue, even in the absence of T cells.[54-57]

Conclusion

The exacerbation of psoriasis in patients with HIV is largely mediated by memory CD8 T cells, a population of cells that are relatively and absolutely expanded in HIV infection. The IFN-γ produced by the memory CD8 T cells is capable of inducing keratinocytes to abnormally express HLA-DR, which predisposes these cells to become activated by bacterial superantigens that are more likely to be in excess in the immunocompromised patient. Once activated, these keratinocytes perpetuate the psoriatic phenotype by producing the proinflammatory cytokine, TNF-α. This tumultuous cycle is important because targeting specific disease mediators has proved to be therapeutic and clinically applicable in patients with HIV and psoriasis.

This article is the first of a 2-part series. The second part, providing a comprehensive, in-depth appraisal of current treatment regimens available to patients with both HIV and psoriasis, will appear in a future issue of Cutis®.

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