

# Disseminated Vitiligo Associated With AIDS

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*We report a case of vitiligo arising one year after human immunodeficiency virus (HIV) seropositivity but before clinical onset of acquired immunodeficiency syndrome (AIDS). To our knowledge, this specific time sequence has not been described. Generalization of such lesions began during a period of medical noncompliance, increasing viral load, rising CD8<sup>+</sup> count, and markedly decreased CD4<sup>+</sup> count. These findings suggest new mechanisms of autoimmune and infectious pathogenesis.*

*Cutis.* 2006;77:169-173.

Vitiligo is an acquired hypomelanotic disorder in which a functional loss of melanocytes manifests grossly as depigmented patches of skin and overlying hair.<sup>1</sup> Although a strong genetic component has been supported by familial clustering, a non-Mendelian, multifactorial inheritance pattern is most likely.<sup>2,3</sup> Specifically, the strong association with noncutaneous autoimmunity implies an equally important nongenetic component to disease.<sup>4,9</sup>

The association of vitiligo with human immunodeficiency virus (HIV) infection may confirm the significance of such environmental queues in pathogenesis. Although rheumatic manifestations of HIV infection have been described,<sup>10-12</sup> vitiligo has been infrequently observed in patients with acquired immunodeficiency syndrome (AIDS); reports of 8 total patients with HIV-associated vitiligo exist in the literature.<sup>13-16</sup> In 6 patients, AIDS-defining illnesses preceded the development of skin lesions.<sup>13,15,16</sup> In one report, a vitiligo exacerbation was noted after highly active antiretroviral therapy

(HAART) was commenced and correlated to a rising CD4<sup>+</sup> count.<sup>16</sup> To our knowledge, we present the first instance of vitiligo arising after HIV seropositivity but before the clinical onset of AIDS. Impressive dissemination of vitiliginous lesions then occurred during a period of profound CD4<sup>+</sup> T-cell lymphopenia, escalating viral load, and increasing CD8<sup>+</sup> count. Such distinct clinical and immune parameters may offer new insight into disease pathogenesis.

## Case Report

A 45-year-old black man was diagnosed with HIV infection in 2001. Within several months of diagnosis, the patient exhibited new-onset, small depigmented macules in a focal distribution on the chest and face, consistent with vitiligo. The patient reported no personal or family history of vitiligo or autoimmune disease. Over the next year, he missed all scheduled follow-up appointments. However, on later questioning, the patient denied any AIDS-defining illness and was otherwise healthy. Then in 2002, approximately one year after HIV seropositivity, he presented to the Dorn Medical Center with a viral load level of 19,347 copies/ $\mu$ L and significant CD4<sup>+</sup> T-cell depletion. The patient was later diagnosed with *Enterococcus faecalis* pneumonia. After a short course of antibiotics, the patient was discharged, and HAART was started.

However, the patient's compliance was questionable. In fact, over the next 3 months, he was hospitalized on 2 separate occasions, once for nocardiosis and more recently for cryptococcal meningitis. During these admissions, the vitiliginous skin lesions were noted to have progressively generalized, comprising an estimated 40% of body surface area. Depigmented macules had apparently coalesced on the patient's arms, chest, and face. Perifollicular skin and overlying hair were spared from depigmentation; at the periphery of the patches, speckling of depigmented and normal skin was observed (Figure 1).

The progression of vitiligo in our patient occurred during a time in which he admitted to medical noncompliance. Consequently, his viral

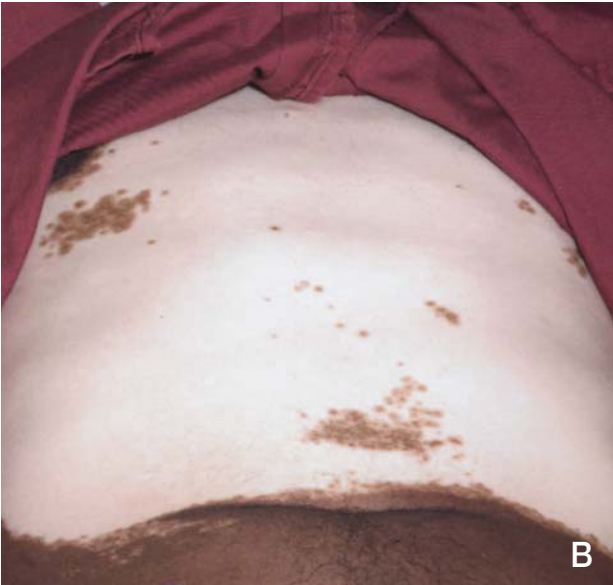
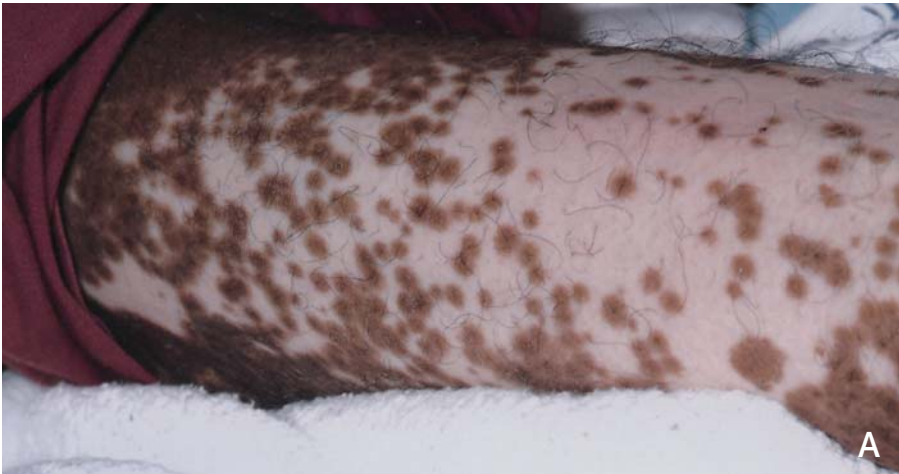
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Accepted for publication March 2, 2005.

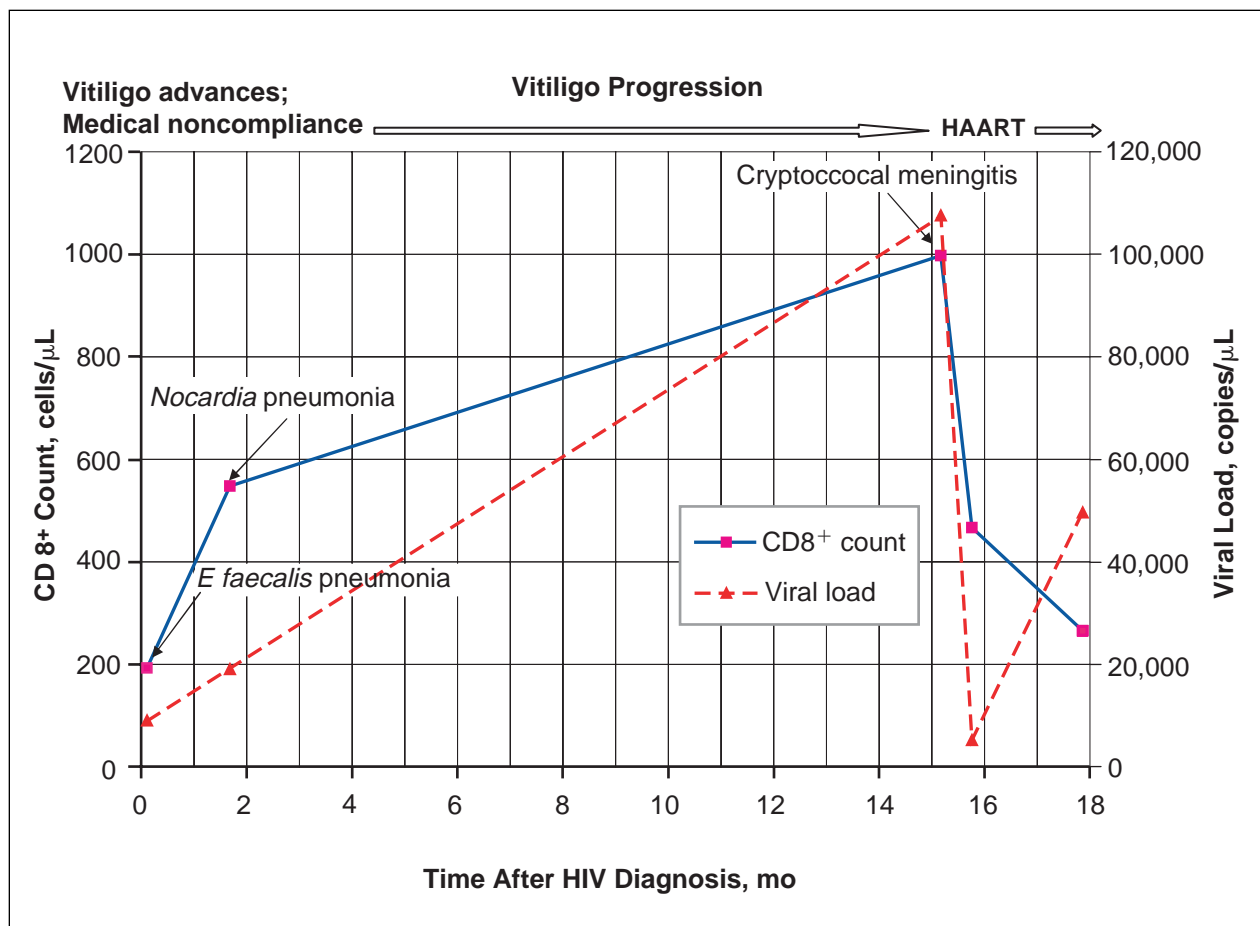
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The authors report no conflict of interest.

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**Figure 1.** Coalescent, depigmented macules in a widespread distribution on the upper extremity (A), trunk (B), and forehead (C). Note the speckling pattern and perifollicular sparing.



**Figure 2.** CD8<sup>+</sup> counts and viral load over the 18-month interval following diagnosis of human immunodeficiency virus (HIV). During this interval, the absolute CD4<sup>+</sup> count fluctuated insignificantly, from 3 to 13 cells/μL, and the CD4<sup>+</sup>/CD8<sup>+</sup> ratio ranged from 0.01 to 0.03. HAART indicates highly active antiretroviral therapy; *E faecalis*, *Enterococcus faecalis*.

load level increased from 19,347 copies/μL to more than 100,000 copies/μL. Figure 2 reflects changes in viral load and CD8<sup>+</sup> T-cell levels. CD4<sup>+</sup> cell count was severely decreased but stationary during this interval. After resumption of HAART, no skin changes or exacerbation of vitiligo was observed. Despite viremic control and reversal of the relative CD8<sup>+</sup> lymphocytosis from 1016 to 270 copies/μL, the CD4<sup>+</sup> cell count remained low (7). Immunoglobulin levels were not obtained.

### Comment

HIV-associated vitiligo was first reported by Duvic et al<sup>13</sup> in 1987. Several mechanisms were proposed to account for pathogenesis in this context: (1) immune disequilibrium among cytotoxic, suppressor, and helper T cells; (2) cellular cytotoxicity against melanocytes; (3) polyclonal B-cell activation; and (4) direct HIV infection of melanocytes.<sup>15</sup> In summary,

immunocompromise fundamental to HIV infection may promote humoral or cell-mediated autodestruction of melanocytes.

Autoimmune pathogenesis in vitiligo unassociated with HIV has been supported by circulating antimelanocyte antibodies and local epidermal infiltration by self-reactive T cells.<sup>17,18</sup> Although a native autoimmune phenomenon is more common in generalized vitiligo,<sup>19</sup> a secondary process may arise in segmental vitiligo when the destruction of melanocytes (by other mechanisms) may incite a potentiating autoreactive response.<sup>20</sup> In 6 of the 8 prior cases, vitiligo onset occurred after AIDS-defining symptomatology.<sup>13,15,16</sup> We propose that severe immunodeficiency (such as that in AIDS) may simulate secondary autoimmunity, resulting in the severe vitiligo seen in these cases; tissue damage during HIV infection may, in fact, expose previously hidden self-antigens, with consequent

autoimmune attack.<sup>21</sup> Moreover, the macrophage and Langerhans cell infiltration seen in vitiliginous skin<sup>22,23</sup> may indicate a role for histiocytes in propagating autoimmunity by efficiently presenting the antigens released by dying melanocytes. This model may thus explain the extensive generalization seen in our case.

In this way, HIV may induce a loss of peripheral tolerance to self-reactive B and T cells. Most persons develop tolerance to autoantigens by low-level expression on antigen-presenting cells or by lack of necessary co-stimulatory molecules. Autoimmune disease arises when loss of such tolerance is induced through molecular mimicry or direct B-cell stimulation.<sup>21</sup> HIV may directly supply cross-reactive viral epitopes that sufficiently saturate antigen-presenting cells to induce autoimmunity against melanocytes. This effect may be especially important when the viral load is high (as in our patient) and when HIV-specific protein turnover increases. HIV also predisposes an individual to opportunistic pathogens whose antigens may encrypt melanocyte-specific protein sequences. Additionally, HIV infection and associated opportunists, eg, Epstein-Barr virus, are polyclonal B-cell mitogens.<sup>24</sup> Specifically, patients with vitiligo have persistent elevations in IgG to Epstein-Barr virus early antigens.<sup>25</sup> Relative to the previous reports,<sup>13,15,16</sup> early-onset vitiligo in our patient may indicate native humoral autoimmunity intensified by an HIV-induced polyclonal B-cell response. Indeed, polyclonal hypergammaglobulinemia is a presenting manifestation of HIV infection.<sup>26</sup>

In cases of vitiligo unassociated with HIV, both increased and decreased CD4<sup>+</sup>/CD8<sup>+</sup> ratios have been observed,<sup>27-30</sup> and the restitution of CD4<sup>+</sup> cells has correlated to the extent of depigmentation in a recent report of HIV-associated vitiligo.<sup>16</sup> Polymorphisms in cytotoxic T-lymphocyte antigen-4, a T-cell surface protein necessary for apoptosis of activated peripheral T cells, have been found among patients with vitiligo.<sup>31,32</sup> Additionally, circulating cytotoxic CD8<sup>+</sup> T cells bearing high levels of skin-homing antigens and autoreactivity against melanocyte-specific proteins have been demonstrated in a significant proportion of vitiligo patients.<sup>33</sup> It is therefore possible that HIV-associated superantigens may select for T-cell clones resistant to apoptosis and cytotoxic to melanocytes. A 5-fold increase in CD8<sup>+</sup> cells in our patient therefore may be an important finding.

Direct viral pathogenesis also is an interesting hypothesis. Indeed, cytomegalovirus DNA isolated from depigmented and perilesional skin in patients with vitiligo may suggest etiologic importance. Interestingly, these patients had a greater incidence

of concurrent autoimmune disease.<sup>34</sup> Additionally, expression of endogenous viral genes by melanocytes may influence the development of autoimmune vitiligo in the Smyth line chicken model.<sup>35</sup> In fact, retroviral integration into genomic DNA has been linked to immune perturbation. Likewise, direct HIV infection of melanocytes may alter the sequence of host-specific antigens through insertional mutagenesis. In a similar manner, viral infection of epidermal histiocytes may enhance antigen presentation by altering major histocompatibility complexes. Such mechanisms may predispose to autoimmunity.

## Conclusion

To our knowledge, we present the first case of vitiligo diagnosed in an HIV-seropositive patient before the clinical onset of AIDS. This distinct time course may suggest underlying humoral autoimmunity enhanced by HIV-associated polyclonal B-cell stimulation. Generalization of skin lesions in our patient was impressive and occurred after progression to AIDS. Lesional expansion correlated to an increasing viral load and CD8<sup>+</sup> count. A drastic increase in CD8<sup>+</sup> cells during this period may implicate T-cell cytotoxicity in pathogenesis, while a severely depleted CD4<sup>+</sup> count may signify a gross disturbance in immunosurveillance. Furthermore, an increasing viral load may indicate a direct cytopathic effect on melanocytes. Nonetheless, vitiligo progression after reinstatement of HAART, restitution of CD4<sup>+</sup> count, and reduction in viral load has been described.<sup>16</sup> Perhaps in the latter case, a clonal expansion of melanocyte-directed T cells resulted in disease exacerbation. In this regard, seemingly paradoxical epiphenomenon of HIV infection may result in autoimmune disease—namely, vitiligo—through different mechanisms. However, a unifying factor among cases may be a loss of immune tolerance secondary to severe immunocompromise.

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