Vitiligo immune reconstitution inflammatory syndrome (IRIS)—An incidental finding in a tertiary teaching hospital in southeast Nigeria

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INTRODUCTION

Skin diseases occur at every stage of HIV infection. They not only act as markers of disease, they may reflect the underlying immune status.[1] An estimated 90% of HIV-infected individuals will have at least 1 dermatologic manifestation during the course of disease.[2-4] These diseases may be infections, noninfectious inflammatory conditions, or neoplasms.[5] Pigmentary abnormalities may occur as a side effect of antiretroviral therapy (ART) itself or from effects of drug treatment of opportunistic infections.

Vitiligo in a patient with HIV/AIDS was first reported by Duvic et al in 1987.[6] Since then, vitiligo has been reported frequently in HIV and may occur as a result of direct viral infection of melanocytes by HIV, polyclonal B-cell activation against melanocytes, production of γ-interferon (toxic to melanocytes), or changes in the balance between helper and suppressor T cells.[6,7] Some researchers postulate that increased numbers of $CD8^+$ cytotoxic T cells in lesional skin and peripheral blood, along with a decrease in $CD4^+$ T cells, leads to an increased $CD8^+/CD4^+$ ratio.[6] Reduced numbers of $CD4^+$ peripheral T cells usually observed in AIDS patients may favor the development of vitiligo.

Although antibodies in vitiligo are commonly directed against melanocyte antigens on the surface of the cells,[8] Kemp et al,[9] using phage display technology with a melanocyte cDNA phage display library, identified melanin-concentrating hormone receptor 1, a surface receptor, as a novel target of autoantibody reactivity in vitiligo patients. Melanin-concentrating hormone receptor 1 autoantibodies in vitiligo patients may have a blocking effect on the functioning of the receptor. We describe a case of vitiligo developing 2 months after commencing highly active antiretroviral therapy (HAART) in a woman infected with HIV.

Abbreviations used:

ART:	antiretroviral therapy
HAART:	highly active antiretroviral therapy
IRIS:	immune reconstitution inflammatory syndrome

CASE REPORT

A 41-year-old female patient (Fig 1) presented to the HIV Treatment Clinic of the University of Nigeria Teaching Hospital, Ituku-Ozalla in April, 2011, with a history of recurrent boils, fever, and intermittent cough, which had been treated with over-the-counter antibiotics. She was screened and found to be positive for HIV infection. Apart from the pyodermas, she had no other significant medical history. She was not diabetic and had no family history of vitiligo or other autoimmune diseases; thus, a genetic predisposition was ruled out.

Her baseline investigations, which included a complete blood count, renal and liver function tests,

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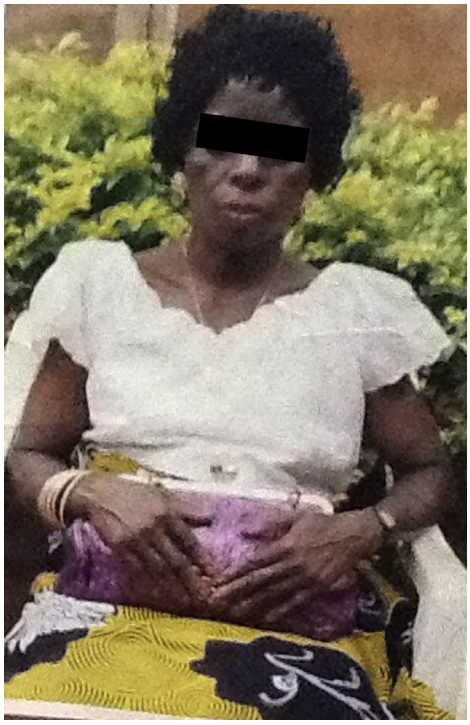

Fig 1. Patient before HAART.

Fig 2. Patient two months after commencing HAART.

and fasting serum lipids, were all normal, as was her chest radiograph. Baseline viral load assay was not carried out before commencement on HAART because viral load assays are not routinely carried out in our facility due to the high cost of running the test. The patient's CD4 cell count was 29 cells/mm^3; thus, she was found to be eligible for HAART according to the National Guideline for HIV treatment at that time. The patient began HAART (tenofovir/lamivudine/nevirapine) on May 9, 2011.

Two months later, fair patches developed on her face. Lesions rapidly became generalized, involving the rest of the body, with associated hair whitening (Fig 2). Physical examination at this time found an anxious, middle-aged woman with stable vital signs and a body mass index of 16.9. She had generalized depigmentation and poliosis. The diagnosis of vitiligo was confirmed by histopathology, which showed complete absence of melanocytes in the basal layer of the epidermis.

Because the depigmentation developed after starting HAART, a diagnosis of vitiligo immune reconstitution inflammatory syndrome (IRIS) was made. Although our patient did not have a baseline viral load assay, our patient had a very low CD4 cell count at initiation of therapy. Severe CD4 T-cell lymphopenia before initiation of HAART was found to be a predictor of IRIS in several studies,[10] and this finding formed part of our rationale for making the diagnosis of vitiligo IRIS in this patient.

Table I shows the patient's baseline investigation results and serial CD4 cell counts/viral load.

The patient has not achieved any repigmentation; generalized depigmentation persists, causing her great emotional distress.

DISCUSSION

Cutaneous disorders associated with HIV infection may weaken self-esteem with resultant depression and suicidal tendencies. Vitiligo is a depigmentary disease characterized by the occurrence of circumscribed white macules in the skin caused by the destruction of melanocytes in the epidermis. It causes severe embarrassment and social isolation, especially in Africans in whom the depigmentation is more obvious. In patients who are already stigmatized by HIV, the psychological distress may become overwhelming.

The etiology is multifactorial, but autoimmunity is implicated in pathogenesis.[11] Persistent viral infections are also postulated to be triggers for the development of autoimmune disease; thus, vitiligo may be an example of an autoimmune disease triggered by viral infection in a genetically predisposed host.[12] Several researchers have reported the occurrence of vitiligo in patients with HIV, either as a result of the infection itself or a complication of ART, with a few of them achieving repigmentation.[12-14]

Table I. Investigation results

Date	Laboratory test	Result
April 11, 2011	Hemoglobin	9.9 G/dL
	$CD4^+$ T cells	29 cells
	Total white blood cell count:	3.1 × 10^6/L
	Differentials:	
	Neutrophils	39%
	Lymphocytes	49%
	Others	12%
	Sodium	135 mmol/L
	Potassium	3.6 mmol/L
	Bicarbonate	27 mmol/L
	Creatinine	0.7 mg/dL
	Urea	8.1 mmol/L
	Fasting blood glucose	94 mg/dL
	Total cholesterol	2.8 mmol/L
	High-density lipoprotein cholesterol	0.6 mmol/L
	Low-density lipoprotein cholesterol	1.1 mmol/L
	Triglyceride	1.1 mmol/L
	Total protein	8.5 g/L
	Albumin	2.9 g/L
	Alkaline Phosphatase	93 U/L
	Alanine aminotransferase	31 U/L
	Aspartate aminotransferase	60 U/L
July 25, 2011	$CD4^+$ T-cells	45 cells/mm^3
January 18, 2012	$CD4^+$ T-cells	105 cells/mm^3
	Viral load	1,562 copies IU/mL
January 16, 2013	$CD4^+$ T-cells	197 cells/mm^3
	Viral load	200 copies IU/mL

The objective of combined ART in immunocompromised HIV-infected individuals is immune reconstitution. ART in HIV/AIDS patients leads to improvement in $CD4^+$ T-cell counts, reductions in plasma viral load, and partial restoration of immune function.[15] However, in certain situations, an abnormal manifestation of this effect occurs—immune reconstitution inflammatory syndrome (IRIS) or immune restoration syndrome—characterized by paradoxical worsening of an existing infection or disease process and manifestation of a new infection/disease process soon after ART initiation.

First accounts of IRIS occurred in patients on zidovudine monotherapy who had fever associated with lymphadenitis and background nontuberculous mycobacterial diseases.[16] Studies find that innate immune dysfunction in the setting of high antigen load plays a role in driving pathologic proinflammatory responses in IRIS.[17] Criteria that need to be fulfilled in making a diagnosis of IRIS include a temporal association between initiation of ART and subsequent development of symptoms (usually within 3 months), evidence of immune restoration, and consistent clinical signs.[15] IRIS may be associated with infectious diseases (eg, bacterial, viral, fungal, and parasitic infections) or noninfectious conditions including autoimmune and inflammatory diseases as well as malignancy.[15]

Certain biomarkers may be predictive of IRIS including C-reactive protein (fungal, cryptococcal, and mycobacterial infections); interleukin-6, interleuking-18, and interferon-inducible protein-10 (viral and mycobacterial infections); and interferon-γ (mycobacterial and fungal infections).[18] However, because our patient was seen in a resource-constrained center without access to sophisticated investigations, no assay for these biomarkers was carried out.

Our patient did not undergo a viral load assay before starting HAART, but 2 subsequent viral load assays found low HIV viral load levels. Her $CD4^+$ T-cell count improved slightly on ART (29 cells/mL^3 to 45 cells/mL^3). Although some studies found repigmentation in patients who had vitiligo in the setting of HIV infection, our patient had total and persistent depigmentation.

ART is effective in reducing HIV viral load to undetectable levels, although it has not been found to have any specific effect on vitiligo. Starting ART does not necessarily lead to resolution of vitiligo, but benefit of therapy is highest when ART is started early in disease, before the onset of severe immunodeficiency. It is important for the clinician to be aware of the possibility of autoimmune diseases presenting as IRIS.[19,20] as these IRIS-related events may fall outside the Centers for Disease Control case definition for HIV-associated and AIDS-defining events. More research is needed to further understand the role of autoimmunity in HIV/AIDS and effective measures that may help in mitigating such responses.

REFERENCES

1. Raju PV, Rao GR, Ramani TV, Vandana S. Skin disease: clinical indicator of immune status in human immunodeficiency virus (HIV) infection. *Int J Dermatol*. 2005;44(8):646-649.
2. Dover JS, Johnson RA. Cutaneous manifestations of human immunodeficiency virus infection. Part II. *Arch Dermatol*. 1991; 127:1549-1558.
3. Dover JS, Johnson RA. Cutaneous manifestations of human immunodeficiency virus infection. Part I. *Arch Dermatol*. 1991; 127:1383-1391.

4. Tschachler E, Bergstresser PR, Stingl G. HIV-related skin diseases. *Lancet*. 1996;348:659-663.
5. Hengge UR, Franz B, Goos M. Decline of infectious skin manifestations in the era of highly active antiretroviraltherapy. *AIDS*. 2000;14:1069-1070.
6. Duvic M, Rapini R, Hoots WK, et al. Human immunodeficiency virus-associated vitiligo: expression of autoimmunity with immunodeficiency? *J Am Acad Dermatol* 1987;17: 656-662.
7. Wang A. Vitiligo in HIV/AIDS: a case report (Poster reference number 5629). *J Am Acad Dermatol*. 2012:AB 181.
8. Cui J, Harning R, Henn M, Bystryn J-C. Identification of pigment cell antigens defined by vitiligo antibodies. *J Invest Dermatol*. 1992;98:162-165.
9. Kemp EH, Waterman EA, Hawes BE, et al. The melanin-concentrating hormone receptor 1, a novel target of autoantibody responses in vitiligo. *J Clin Invest*. 2002;109(7): 923-930.
10. Murdoch DM, Venter WD, Feldman C, Van Rie A. Incidence and risk factors for the immune reconstitution inflammatory syndrome in HIV patients in South Africa: a prospective study. *AIDS*. 2008;22:601-610.
11. Sandoval-Cruz M, García-Carrasco M, Sánchez-Porras R, et al. Immunopathogenesis of vitiligo. *Autoimmun Rev*. 2011;10: 762-765.
12. Gaurkar SP, Parmar KS, Shah BJ. Letters to the Editor-Sequential development of psoriasis, alopecia universalis, and vitiligo vulgaris in a human immunodeficiency virus seropositive patient: A unique case report. *Indian J Sex Trans Dis*. 2014;35(2):167-169.
13. Xuan L, Baohua Y, Lan L. Alopecia areata and vitiligo as primary presentations in a young male with human immunodeficiency virus. *Indian J Dermatol*. 2014;59:209.
14. Defo D, Kouotou EA, Bissek AC, Mboua JB. A case of vitiligo occurring after initiation of antiretroviral treatment and disappearing during this treatment: autoimmune IRIS syndrome? *Ann Dermatol Venereol* 2012;139(11):736-738.
15. Sharma SK, Soneja M. HIV & immune reconstitution inflammatory syndrome (IRIS). *Indian J Med Res*. 2011;134(6):866-877.
16. Jacobson MA, McGrath MS, Joseph P, Molaghan JB, Tadepalli S, Quinn R. Zidovudine-induced fever. *J Acquir Immune Defic Syndr*. 1989;2(4):382-388.
17. Walker NF, Scriven JMeintjes G, Wilkinson RJ. Immune reconstitution inflammatory syndrome in HIV-infected patients. *HIV AIDS (Auckl)*. 2015;7:49-64.
18. Sereti I, Rodger AJ, French MA. Biomarkers in immune reconstitution inflammatory syndrome: signals from pathogenesis. *Curr Opin HIV AIDS*. 2010;5(6):504-510.
19. O'Leary JG, Zachary K, Misdraji J, Chung RT. De novo autoimmune hepatitis during immune reconstitution in an HIV-infected patient receiving highly active antiretroviral therapy. *Clin Infect Dis*. 2008;46:e12-e14.
20. Ferrand RA, Cartledge JD, Connoly J, Standish RA, Miller RF. Immune reconstitution sarcoidosis presenting with hypercalcaemia and renal failure in HIV infection. *Int J STD AIDS*. 2007;18:138-139.