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Human immunodeficiency virus–associated vitiligo: Expression of autoimmunity with immunodeficiency?

Madeleine Duvic, M.D.,* Ronald Rapini, M.D.,* William Keith Hoots, M.D.,*** and Peter W. Mansell, M.D.,****
Houston, TX

Persistent viral infections have been postulated to be trigger factors for the development of autoimmune disease. We report the development of vitiligo in four patients with human immunodeficiency virus (HIV)—related conditions and in one patient with hepatitis who later developed both psoriasis and acquired immunodeficiency syndrome (AIDS). Other common features were hepatitis and multiple other viral infections. Ribavirin was associated with repigmentation in one patient. Vitiligo may be an example of an autoimmune disease triggered by viral infection in a genetically predisposed host. (J AM ACAD DERMATOL 1987;17:656-62.)

From the University of Texas Health Science Center at Houston, Medical School, The M.D. Anderson Hospital and Tumor Institute, Departments of Dermatology* and Internal Medicine*** and Pediatrics,**** and the Institute for Immunologic Disorders.*****

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Reprint requests to: Dr. Madeleine Duvic, Department of Dermatology, University of Texas Medical School, 6431 Fannin, MSB 1.204, Houston, TX 77030.

The human immunodeficiency virus (HIV), by infecting the helper T cell and other CD4+ cells, causes immunodysfunction and finally immunodeficiency, the most severe form of which is AIDS, the acquired immunodeficiency syndrome. Early HIV infection is associated with immune hyperstimulation (lymphadenopathy, polyclonal B cell activation with hypergammaglobulinemia, activated T suppressor cells (T8+, Ia+), while AIDS patients have loss of T4 and Langerhans cells, diminished antigen response, interleukin 2 and gamma interferon production, and virus-specific cytotoxicity. Viral infections, especially herpes simplex, activate HIV-infected cells.

In the course of caring for the dermatologic problems of HIV+ positive patients, we were...
struck by the coincidence of seeing five patients over a short period of time who developed vitiligo while evolving AIDS-related complex (ARC) or AIDS. Four are reported here; the fifth was lost to follow-up. An additional AIDS patient gave a history of developing vitiligo and hepatitis concurrently, probably long before getting HIV infection. Vitiligo has not previously been reported in association with viral infections or HIV. If more than a coincidence, it suggests that viruses may indeed serve as a trigger factor for the autoimmune disease, vitiligo.

METHODS AND CASE REPORTS

Patients attended the clinical immunology and dermatology outpatient clinics at M.D. Anderson Hospital, The University of Texas System Cancer Center. We have followed over 1000 patients with ARC and AIDS, of whom about half had had symptomatic cutaneous complications during the preceding 3 years. Patients were tested for HIV by enzyme-linked immunosorbent assay (ELISA), followed by Western blot. Those receiving experimental drugs signed informed consent and the protocols were approved by the institutional review board.

CASE REPORT AND DESCRIPTIONS

Case 1

A 35-year-old male homosexual developed ARC (AIDS-related complex) in January 1983 after multiple infections, including mumps, Coxsackie virus, hepatitis, and syphilis. He received azimexon (BM 12,531) with stable symptoms until December 1985, when he developed fever, fatigue, and night sweats. At the same time he noted white patches in the scalp and beard hair and on the extensor surfaces of the arms and back (Fig. 1). His evaluation showed T4/T8 ratio of 0.29, anergy to skin tests, and markedly elevated cytomegalovirus and Epstein-Barr virus titers (Table I). Hepatitis B core antibody and HIV tests showed positive results.

Ribavirin (1-beta-ribofuranosyl-1,2,4,-riazole-3-carboxamide) was begun at 800 mg three times daily for 7 days, and then daily for 23 weeks. He developed a photosensitivity eruption after 6 weeks. At 12 weeks
Table I. Laboratory abnormalities in AIDS-associated vitiligo

| Case | T4: T8 ratio or T4 count | Total protein | Platelets | WBC count | Skin tests | HIV | CMV |
|------|-------------------------|---------------|-----------|-----------|-------------|-----|-----|
| 1    | 0.17                    | 8.1           | 174       | 3,000     | Anergy      | +   | 1:512 |
| 2    | 380/mm³, IgG = 2529     | 9.9           | ND        | 12,300    | Anergy      | +   | 1:64 |
|      | 0.2                     |               |           |           |             |     | GP 24 |
|      |                         |               |           |           |             |     | GP 41 |
| 3    | 320/mm³                 | ND            | ND        | 7,800     | Anergy      | +   | 1:2048 |
| 4    | 64/mm³                  | 6.7           | 63        | 2,800     | Anergy then moderate reaction on AZT spring 1987 | +   | 1:128 + cultures urine, sputum |
| 5    | Decreased               | ND            | 296       | 1,500     | Anergy      | +   | 1:64, sputum + |

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; GP: glycoprotein antigens of 24 and 41 kd; HIV: human immunodeficiency virus; LFTs: liver function tests; ND: not determined; WBC: white blood cell count.

Table II. Clinical features of AIDS-associated vitiligo

| Case | Age | Sex | Risk | Existing and past infections | Onset and course | Features/course | Onset HIV and course |
|------|-----|-----|------|-------------------------------|-----------------|----------------|---------------------|
| 1    | 35  | M   | HS   | Mumps; 2° syphilis 1980; hepatitis | December 1985   | Patient had ARC symptoms: hair and beard turned white, and later vitiligo on forearms; ribavirin reversal | 1/83, ARC |
| 2    | 4   | M   | TR   | Bilateral parotiditis 12/85   | December 1985   | Depigmentation acral digits and arms with onset of ARC symptoms | 12/85, ARC; diarrhea, fever, weight loss |
| 3    | 38  | M   | HS   | Parotiditis 1967; mononucleosis; hepatitis 1977 | December 1986   | Depigmented 2 × 3-cm macules in 4/86; developed alopecia areata on ribavirin | 1984, ARC symptoms; 10/85, HIV +; 1/86, AIDS |
| 4    | 39  | M   | HS   | Mumps, childhood; chickenpox, child; hepatitis 1968; chronic HSV 1977 | February 1987   | Guttate hypomelanotic lesions on chest suddenly appeared in patient with CMV, chronic HSV, zoster | 1981, lymphadenopathy; 7/86, HIV +; 8/86, AIDS |
| 5    | 42  | M   | HS   | Hepatitis 1970; syphilis       | With hepatitis 1970 | Large areas of vitiligo started genitals and on thighs 4 years later; psoriasis in vitiligo appeared | 6/84, ARC; 10/84, AIDS; 10/85, expired |

ARC: AIDS-related complex; CMV: cytomegalovirus; HIV: human immunodeficiency virus; HS: homosexual; HSV: herpes simplex virus; MAC: Mycobacterium avium complex; PCP: Pneumocystis carinii pneumonia; TR: transfusion.

repigmentation hair and skin lesions began; he continued to take ribavirin and showed improvement.

Case descriptions

The other cases are summarized in Table II. Patients 1 to 3 developed vitiligo within 2 years of HIV symptoms. Patient 2, a child with transfusion-induced ARC, developed acral vitiligo (Fig. 2) at the same time he developed parotiditis, fever, diarrhea, weight loss, and hypergammaglobulinemia.

Patient 3 developed 1- to 2-cm areas of vitiligo in the month following disseminated herpes zoster. These were not in previous zoster lesions, nor was inflammation noted. Three weeks after starting ribavirin he developed alopecia areata. Repigmentation did not occur in the skin.

Patient 4 had multiple persistent and chronic viral infections, including herpes simplex, for 10 years and had recent episodes of herpes zoster. In February 1987 three depigmented 1 × 2-cm macules appeared sud-
some form of viral hepatitis. There was evidence for previous hepatitis A and hepatitis B, as well as viral inclusions, on biopsy suggestive of non-A, non-B hepatitis. All five patients shared serologic evidence of viral hepatitis and had elevated liver enzymes in association with vitiligo.

**DISCUSSION AND COMMENTS**

The incidence of vitiligo in the general population has been estimated at 1% to 2%. Although four vitiligo cases among several hundred HIV+ persons is not higher than expected, we rarely see new-onset vitiligo and found the coincidence of seeing four cases within months quite remarkable. Furthermore, premature graying, suggested related to vitiligo by Lerner and Nordlund,17 is quite common as ARC patients progress to AIDS. Thus, if HIV infection and vitiligo are related, HIV, its opportunistic viruses (especially hepatitis), or dysimmunity may trigger vitiligo in the genetically predisposed host.

Evidence for a relationship between the immune system and vitiligo exists. Immunodeficiency and vitiligo have been reported in the setting of mucocutaneous candidiasis. Indeed, patients with mucocandidiasis without vitiligo may have circulating antimelanocyte antibodies.3-13 “Partial albinism” and vitiligo in association with fever, pyogenic infections, hypogammaglobulinemia, and reduced Langerhans cells were reported in two patients from the 1960s and 1970s.29 Finally, the Vogt-Koyanagi-Harada syndrome, a viral-like illness with aseptic meningitis, hair loss, uveitis, dysacusia, and vitiligo, has a specific HLA class II antigen LDWα and antibodies cytotoxic to melanocytes.18,19,20 Similar antibodies have also been found in vitiligo patients.17

The mechanism of autoimmunity (in this case vitiligo) is unknown. We suggest that the following possibilities exist and could be tested experimentally.

1. Direct viral infection of melanocytes. HIV infects central nervous system astrocytes and oligodendrocytes.31 Melanocytes as neural crest cells might also be capable of infection. We could not find melanocytes in our biopsy to test this hypothesis.

*Duvic, M. Unpublished observation, 1986.*
Fig. 3. Case 4. Biopsy from the hypopigmented lesion (A) shows reduced melanocyte granules compared with normal skin (B). There is mild epidermal atrophy in both.
(Fontana stain; x300.)

2. Nonspecific polyclonal B cell activation with production of autoantibodies. Human immunodeficiency virus and Epstein-Barr virus both induce this.\textsuperscript{32,33}

3. Cellular cytotoxicity against melanocytes. This could occur through activated cells (present in ARC)\textsuperscript{34,35} and/or through cytokine production (especially gamma interferon).\textsuperscript{36} Gamma interferon is produced in response to viruses and induces aberrant DR expression on epidermal cells.\textsuperscript{37-39} Aberrant DR expression on epidermal cells can induce a cellular immune reaction and could theoretically damage melanocytes.\textsuperscript{40}

4. Changes in the balance between helper, suppressor, and cytotoxic cells due to T cell retrovirus infection.\textsuperscript{34,35}

5. Molecular mimicry between viral antigens and HLA antigens or expression of new antigens as viruses bud from infected cells.\textsuperscript{41}

6. Combinations of the above.

ARC-associated thrombocytopenia is a well-documented example of HIV-associated autoimmune disease. Destruction of platelets is due to an antibody that reacts with a 25,000 dalton platelet-associated protein and cross-reacts with herpes simplex-infected cells.\textsuperscript{42} If similar antimelanocyte antibodies are being produced with antiviral cross-
reactivity, this could explain vitiligo in these reported patients.

If more than coincidental, the development of vitiligo following viral infections such as hepatitis, HIV, herpes zoster or herpes simplex, and cytomegalovirus would support the previous hypothesis that viruses trigger autoimmunity.\textsuperscript{4,43} Vitiligo could be the second reported autoimmune disorder occurring in the setting of the human immunodeficiency virus.

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ABSTRACTS

Comparative characteristics of sources of infection in patients with gonorrhea and syphilis
Korobeinikova EA, Zelenina OL, Alexeeva BA, Popova SN, Novikov VM: Vestn Dermatol Venerol 1986;5:59-61 (Russian)

Data of a sociologic investigation of sources of gonorrhea and syphilis based on an analysis of a questionnaire filled in by the patients are as follows. Gonorrhea patients tended to be younger, to have started to have sexual intercourse at an earlier point in life, and were more likely to be female (67.8%). Syphilis patients tended to be single and male (55%) [Editorial note: the authors do not mention homosexuality as a factor] and were more likely to be unemployed, unskilled workers with a low educational level. Yehudi M. Felman, M.D.

Schulman's eosinophilic fasciitis: news in diagnosis and treatment
Shaposhnikov OK, Rodionov AN, Samtsoev AV: Vestn Dermatol Venerol 1986;5:4-5 (Russian)

A 48-year-old female patient with eosinophilic fasciitis of the face, cheek, neck, shoulders, and trunk responded well to treatment with d-penicillamine, 150 mg b.i.d. for 2 weeks. The authors believe, on the basis of relative and absolute increase in T lymphocytes and immune complement, that immune factors play a role in the pathogenesis of the disease. They also advocate the use of ultrasonic examination in making the diagnosis, as the thickening and induration of the fascia can show up on the scan. Yehudi M. Felman, M.D.

Histocompatibility antigens in psoriasis
Erdes S, Yakovleva DB, Razumnik ID, Mordovstev VN: Vestn Dermatol Venerol 1986;5:8-9 (Russian)

Fifty patients with psoriasis (20 with psoriasis vulgaris and 30 with arthropathic psoriasis) were examined for A and B locuses of the human lymphocyte antigen (HLA) system. An increase in HLA-B13 and HLA-B15 antigens was observed, and the presence of HLA-B13 increasing the risk of psoriasis ninefold, compared to subjects in whom this antigen was not detected was noted. Yehudi M. Felman, M.D.

Coadjuvant therapy with auranofin in the treatment of South American pemphigus foliaceus: a double-blind study
Auada A, Auad T, Auad A, Auad P: Anais Bras Dermatol 1986;61:131-4 (Portuguese)

Twenty-one patients with South American pemphigus foliaceus were divided into two groups. Eleven were treated only with corticosteroids, while 10 also were treated with auranofin (gold), 6 mg daily. After 1 year the gold-treated group required a medium dose of only 5.5 mg daily of corticosteroids for maintenance, whereas the non-gold-treated group required 36.5 mg. Both groups were on an average of 40 mg corticosteroid daily at the start of the study. Yehudi M. Felman, M.D.

Chromate eczema in the food, domestic and cleaning industries
Weiler KJ, Russel HA: Derm Beruf Umwelt 1986;34:135-9 (German)

No chromium in the form of chromate was found in flour and baking powders. Contradictory reports published elsewhere have not been substantiated. The occasional incidence of chromate allergy observed in the domestic services trades, bakeries, curing houses, and bottling plants were found to be due to traces of chrome in the following substances: wood ash, 0.23 ppm, lignite ash, 0.05 to 1.7 ppm, refractory brick, 0.5 to 0.9 ppm, certain alkaline scouring agents, 0.1 to 0.2 ppm, suds produced when washing chrome-containing glasses, 0.13 to 1.61 ppm. Yehudi M. Felman, M.D.