Chronic Diffuse Dermatitis and Hyper-IgE in HIV Infection

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Diffuse dermatitis and markedly elevated serum IgE concentrations were observed in three adult males who were seropositive for human immunodeficiency virus (HIV) antibody. The clinical features in common for these patients included 1) an adult onset of greater than 6 weeks' duration associated with pruritis, 2) T-helper (CD-4) cell depletion, 3) the lack of overt atopic disease, and 4) the lack of opportunistic infection (except oral thrush) and neoplasia. The mean serum IgE concentration was 5 959 (range: 4 930–6 260) IU/ml. Cutaneous involvement consisted of hyperpigmented papules with variable excoriations and lichenification. Zidovudine was administered to all 3 patients and was associated with cutaneous improvement. Serum IgE concentrations from 19 AIDS patients without cutaneous disease did not show significant elevations. These observations suggest that certain patients with HIV infection can manifest a unique hyper-IgE syndrome associated with diffuse cutaneous disease. *Key words: Immunoglobulin E; Acquired immunodeficiency syndrome.* (Received January 15, 1988.)

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There are numerous causes for cutaneous abnormalities in human immunodeficiency virus (HIV) infection. These include manifestations related to hypersensitivity reactions which appear to be increased (1) in patients with the acquired immune deficiency syndrome (AIDS). Few reports have identified either increased atopic manifestations or significant abnormalities in immunoglobulin E (IgE) concentrations in this population. In this report, an association between chronic dermatitis and hyper IgE is described in three patients with seropositivity for HIV antibody.

CASE REPORTS

Case 1

A 25-year-old Black male Honduran was admitted to Metropolitan Hospital (MH) in May 1986 for intermittent fever and malaise persisting 1.5 years and shortness of breath for 1 month. On admission his temperature was 39.2°C. Petechiae of the soft palate, oral thrush, a tonsillar exudate, prominent inguinal adenopathy, and mild right upper quadrant tenderness were noted. Laboratory examination revealed hemoglobin 8.8 g/dl and white blood cell count (WBC) of 4 900/mm^3 with 12% lymphocytes. Erythrocyte sedimentation rate: 120 mm/h (Westergren). Chest X-ray, and a bone marrow examination also normal. The patient made an uneventful recovery and was discharged on ferrous sulfate only.

He was readmitted to MH in January 1987 for fever and painful adenopathy of 3 days' duration. His temperature was 39.7°C. At that time, prominent adenopathy in the anterior/posterior cervical, inguinal, epitrochlear, femoral, and axillary regions was noted as was splenomegaly. On all extremities and the thorax, there was lichenification and focal areas of hyperpigmented papules (Fig. 1) which the patient claimed were pruritic. WBC was 4 100/mm^3 with 23% lymphocytes and 17% eosinophils. A right epitrochlear lymph node biopsy showed diffuse reactive hyperplasia. The patient improved spontaneously and was discharged.

In March 1987 he was readmitted with complaints of fever and productive cough of 4 days' duration. His temperature was 38.9°C, and he had injected conjunctiva and oral pharynx associated with lip

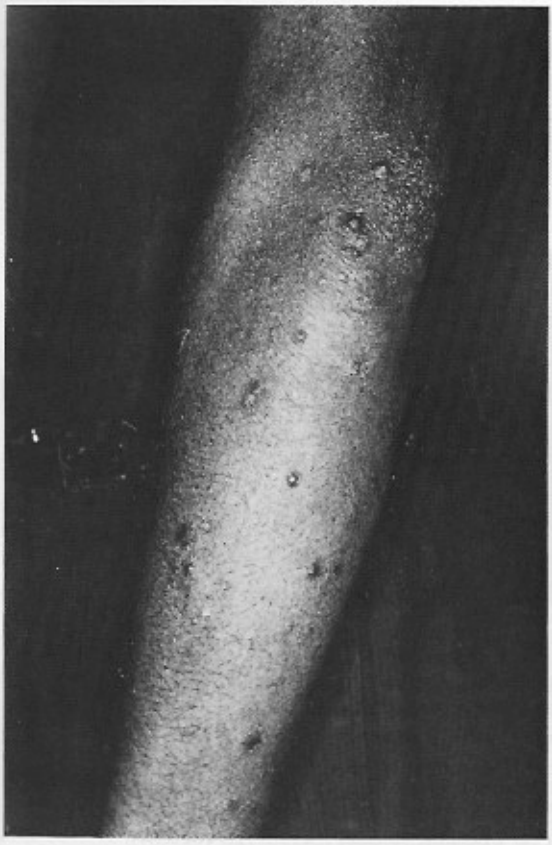

Fig. 1. Hyperpigmented papules on left arm in case 1.

edema. Arterial blood gases revealed resting hypoxemia and a bronchoscopic lavage was positive for *Herpes simplex* and alpha streptococcus. The Epstein-Barr Capsid Antigen antibody was reactive to a titer of 1:80 (normal less than 1:20). The CMV antibody was 1:4 and toxoplasmosis IFA titers were 1:64. The cerebrospinal fluid was unremarkable. The patient was treated with pentamidine and cefamandol, the former being discontinued after the bronchial lavage failed to identify *Pneumocystis carinii*. The patient recovered after a 2-week hospitalization and was discharged to clinic.

In clinic the patient underwent a skin biopsy of one of the papules which showed superficial and deep perivascular infiltrates consisting of lymphocytes, plasma cells, and eosinophils. There was significant hyperkeratosis and rete ridge elongation. This was interpreted as psoriasiform in appearance. Serum IgG was 1660 mg/dl; IgA, 1370 mg/dl; IgM, 203 mg/dl; IgE, 6262 IU/ml; T4 (CD-4) cell count, 4/mm^3; T8 (CD-8) cells, 203/mm^3. Antibody to HIV was positive but antibodies for HIV-2 were negative (kindly performed by Dr Mark Kaplan). HBsAg was positive. A panel of aeroallergen (Center Laboratories NY: 1000 PNU/ml extracts of grass, weeds, trees, ragweed, molds, and house dust) immediate type skin tests (intradermal) proved negative, but with a positive codeine control wheal. The patient denied any atopic conditions. In early August 1987, the patient was treated with zidovudine 200 mg every 4 h and has had decreased pruritis and complete resolution of lichenification on his torso and upper extremities. He requires no cutaneous medications.

Case 2

A 39-year-old Hispanic male was first seen at the MH emergency room in October 1986 for a rash on both arms and the face, associated with pruritis. There were erythematous papules and excoriations on both hands, and a vaguely defined rash on the face was noted at the time. At another hospital, the patient had been treated with penicillin injections for syphilis. In April 1987 he was seen again in the emergency room for a rash involving his trunk and extremities. Hyperpigmented papules with small ulcerations were noted on the back, arms, and groin areas. Cervical lymphadenopathy was noted. He denied any atopic disease.

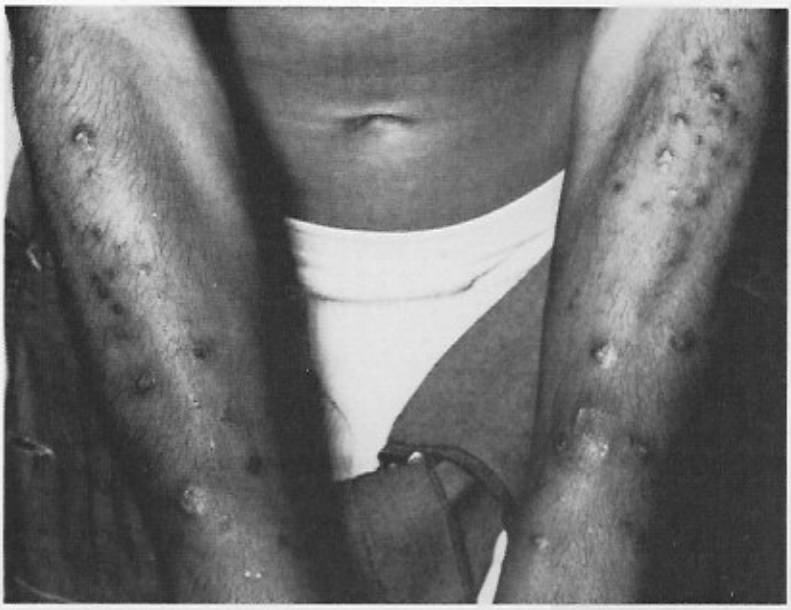

Fig. 2. Hyperpigmented papules on arms in case 2.

He was then again seen in the emergency room for a rash in September 1987, for which he was referred to clinic. Multiple papules associated with some excoriations and ulcers were noted on the arms, face, legs, and trunk (Fig. 2). There were dishydrotic features of the hand dermatitis and there was a malar distribution to the face lesions. Superficial punctate keratitis and oral candidiasis were noted. Methylcellulose, neosporin ophthalmic solution, oral nystatin, and corticosteroid creams were prescribed. Hemoglobin was 12.4 g/dl and the WBC was 5 200/mm^3 with 19% lymphocytes and 6% eosinophils. The T4 (CD-4) lymphocyte count, 8/mm^3; T8 (CD-8) count, 464/mm^3; serum IgE concentration, 6 687 IU/ml; the serum IgG, IgA, and IgM levels, 3 150, 339, and 172 mg/dl respectively. Antinuclear antibody was not detected. A VDRL was positive 1 : 2 and the FTA was positive 1 : 1. Antibody to HIV was positive. Stool examinations for ova and parasites proved negative. A skin biopsy showed hyperkeratosis, parakeratosis, and a perivascular lymphohistiocytic infiltrate with some areas containing many eosinophils. This was interpreted as consistent with a psoriasiform dermatitis. No spirochetes were identified. The oral candidiasis and keratitis resolved but the dermatitis persisted. A panel of aeroallergen extracts (same as in case 1) were applied to test for immediate type hypersensitivity, but proved unreactive. In October 1987, zidovudine 200 mg every 4 h was prescribed. Subsequently the patient has had a decrease in pruritis and has not had any new cutaneous lesions.

Case 3

This case has been reported previously, except for the histopathology (2) and will be only briefly described herein. A 39-year-old Black male with a history of intravenous drug abuse was admitted to MH in March 1987 for treatment of infection of the left third finger. He denied atopic disease—other than penicillin allergy.

In November 1985 he had developed a progressive rash over his upper and lower extremities, face and trunk, which was diagnosed as eczema and treated with corticosteroid creams, with slight improvement. A prior physical examination in 1980 showed normal skin. In March and May 1986, he was treated for blepharoconjunctivitis and a staphylococcal abscess of a lower extremity respectively. The serum IgE concentration was 2 308 IU/ml.

On admission to MH the patient had a temperature of 38.1°C, supraclavicular and inguinal adenopathy, and a fluctuant tender swelling of the distal left third finger. A somewhat broad nasal bridge associated with hypopigmentation, and diffuse and focal areas of lichenification over the entire body with some excoriations and dark papules on the lower extremities were noted. Areas on the scalp showed focal alopecia and raised lichenified papules. The WBC was 4 100 mm^3 with 37% lymphocytes and 10% eosinophils. Flow cytometric analysis revealed 106 T-4 (CD-4) cells and 766 T-8 (CD-8) cells. The serum IgG, IgM, and IgA concentrations were 3 050, 403, and 300 mg/dl, respectively. A skin biopsy showed hyperkeratosis and orthoparakeratosis, with elongation of the rete pegs and some lymphohistiocytic in-

filtrates in the upper dermis. There was spongiosis of the dermis. The same panel of aeroallergen extracts were employed for intradermal skin testing, but showed no immediate hypersensitivity responses. No ova or parasites were identified in the stool.

The patient was treated with incision and drainage of the abscess, and with intravenous antibiotics; he made an uneventful recovery. Zidovudine 200 mg every 4 h was prescribed early in September 1987 and the patient has not had any further bacterial infections. The rash has improved most markedly on the face, with a diminution of the pruritis. The most recent IgE level was 4571 IU/ml.

Studies of IgE in other patients with HIV infection

Nineteen patients with AIDS or ARC (aids-related complex) at this institution without cutaneous disease were assessed for serum IgA, IgG, and IgE concentrations. The mean concentration of IgE was 69.9±78.7 IU/ml. No correlation, as assessed by Spearman's rho-test, was found between IgG and IgE levels. However, serum IgE and IgA concentrations were found to be significantly correlated (p=0.0069).

DISCUSSION

Many dermatologic manifestations are seen in HIV infection and have been recently reviewed (3). These include infectious manifestations such as those due to fungal, treponemal, viral, arthropodial, bacterial, and mycobacterial infections, as well as non-infectious processes. Malignant manifestations include Kaposi's sarcoma and lymphoma lesions, whereas non-malignant lesions include psoriasis/Reiter's syndrome (4–6) and seborrheic dermatitis. The occurrence of Reiter's syndrome in HIV infection has led to a re-examination of the nature of this disorder's pathophysiology with respect to T cell/cellular immunity related disturbances (5). There is some speculation that psoriasis and Reiter's syndrome may have a viral etiology and under circumstances in which immunosuppression occurs, immunoderegulation or derepression allows for viral proliferation and/or triggering of a proliferative and inflammatory response in the skin (6–8).

Atopic dermatitis and the hyper-IgE syndrome are disorders that manifest T lymphocyte abnormalities (9–12). Both conditions have diminished peripheral blood suppressor cells, which has led some investigators to suggest that the high IgE levels seen in both disorders are due to defective IgE-specific suppression (13). Furthermore, a defect in suppressor/cytotoxic CD-8 cell induction by helper/inducer CD-4 cells from atopic dermatitis patients has been demonstrated (14). There have been recent reports of atopic disease occurring in HIV-infected patients (15, 16) after the diagnosis of HIV infection had been established. In one report (16), atopic disease showed improvement on administration of γ-interferon. The implication of this report is that cellular immunity is involved in regulating atopy. Another study showed that leukocyte histamine release by candida and herpes simplex was increased in AIDS patients, implying a potential role for type I hypersensitivity in some types of HIV infection (17).

Diffuse lichenification (such as that seen in case 1) has been described in some AIDS/ARC patients by Farthing et al. (18). However, the 3 patients described here manifested primarily papular lesions which were dissimilar to the fine papular eruptions described in HIV infection by James et al. (19). Another disorder associated with eosinophilia and dermatitis in HIV infection is eosinophilic pustular folliculitis (20). No evidence of this disorder was seen in our patients.

The histopathology of all 3 patients showed significant hyperkeratosis, variable parakeratosis, and some dermal mixed infiltrates. Two patients (nos. 1 and 2) were interpreted as having psoriasiform dermatitis, while pat. no. 3 also manifested significant hyperkeratosis and some elongation of the rete pegs. No clinical manifestations of classical psoriasis or Reiter's syndrome were noted in any of the patients, however. The histopathology of the 3 cases did not demonstrate any characteristics of psoriasis such as stratum corneum absence, Monro microabscesses, or significant dermal papillae blunting (21).

The relationship between serum IgE concentrations and IgA, IgM, and IgG concentrations has been studied in other investigations and no significant relationships were noted (22). However, in the patients without cutaneous disease studied herein, a significant relationship was found between IgA and IgE levels, which may possibly be related to a common process affecting the adjacent alpha and epsilon heavy chain genes' switching mechanism (23), or which relate to immune potentiators/stimuli which are selective for IgA and IgE production. IgE levels in normal populations have not been reported to have any relationship with IgA levels (24). In these 3 patients, however, the IgE concentration was far greater than that seen in the AIDS/ARC patients studied. The reasons for this are not clear. Genetic influences on IgE levels are well described and certain individuals may be genetically predisposed to develop extreme elevations under conditions where there is immunosuppression. Indeed, elevations of IgE levels have been described with cytotoxic treatment and in certain malignancies associated with immunosuppression (25, 26). However, this degree of hyper IgE and its association with chronic dermatitis have not been previously reported in HIV infection.

The patients described in this report showed a remarkable combination of adult onset chronic dermatitis, HIV antibody presence, T helper cell depletion without identifiable invasive opportunistic infection, an extremely elevated IgE concentration, and the lack of apparent immediate hypersensitivity to common aeroallergens. Clinical improvement on zidovudine raises the possibility that this phenomenon is related to immunodysregulation due to infection by HIV.

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