An Erythematous Maculopapular Eruption in Macaques Infected With an HTLV-III-Like Virus (STLV-III)

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A cutaneous maculopapular eruption has been previously described in humans infected with HTLV-III/LAV, the etiologic agent of acquired immunodeficiency syndrome. In this study, rhesus monkeys were prospectively examined after infection with an HTLV-III-like virus (STLV-III) to ascertain the incidence and clinical course of gross and histologic alterations of the skin. Between 1-3 weeks after inoculation, 83% of infected animals developed a transient cutaneous maculopapular eruption of the face, groin, and trunk. Histologically, the affected skin was characterized by a superficial perivascular infiltrate of mononuclear cells with associated endothelial cell hypertrophy and degeneration. This eruption preceded opportunistic infections, neoplasms, and other overt clinical signs commonly associated with an immunodeficiency syndrome. The findings suggest that STLV-III infection in the rhesus monkey closely simulates that which occurs in HTLV-III-infected individuals, and that the skin may represent a site of altered immunoregulation early in the course of this disease. J Invest Dermatol 87:674-677, 1986

**Abbreviations:**
- AIDS: acquired immunodeficiency syndrome
- ARC: AIDS-related complex
- DHR: delayed hypersensitivity response
- ELISA: enzyme-linked immunosorbent assay
- HTLV-III: human T lymphotropic virus type III
- LAV: lymphadenopathy-associated virus
- PBL: peripheral blood lymphocytes
- Pt: postinoculation
- STLV-III: simian T lymphotropic virus type III

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successfully for growth of STLV-III [1], while macaque retrovirus D/New England preferentially replicates in Raji cells, a B-cell line [9]. Serum from each animal also did not reveal antibodies to cell surface antigens of STLV-III- and type D-infected cells using indirect immunofluorescence on infected HUT-78 and Raji cells. Last, the animals were confirmed to be negative for antibodies to STLV-III and type D structural proteins using an enzyme-linked immunosorbent assay (ELISA).

The 12 macaques were divided into 3 groups of 4 animals each and inoculated i.v. with filtered supernatant from cultures of STLV-III-infected HUT-78 cells. This supernatant had a reverse transcriptase activity of 114,000 cpm/ml (assayed as described [1]). Group 1 animals received 1.0 ml of undiluted supernatant; group 2 animals received 1.0 ml of a 1:50 dilution of supernatant, and the animals in group 3 received 1.0 ml of a 1:1000 dilution. The STLV-III virus used in this study was isolated from a rhesus monkey (Mm 251-79) which died of a poorly differentiated lymphocytic lymphoma. The control animals were inoculated i.v. with 1.0 ml of undiluted supernatant from uninfected HUT-78 cell cultures. The animals were observed daily for cutaneous abnormalities. Physical examinations and complete blood counts were performed bimonthly on the STLV-III-inoculated macaques and monthly on the controls. Blood was also drawn bimonthly in the cohort animals for virus isolation and serology. Small wedge biopsies (1.0 cm x 0.5 cm) were obtained surgically from the skin of the medial thigh from group 1 and control animals at 3, 6, and 12 weeks postinoculation (PI). Each sample was divided so that one portion was fixed in 10% neutral buffered formalin and the other in 3% buffered glutaraldehyde. Formalin-fixed tissue was routinely processed, and the sections were stained with hematoxylin and eosin. Glutaraldehyde-fixed samples were washed in phosphate buffer, dehydrated, and embedded in Epon 812 from which 1-μm sections were cut and stained with toluidine blue.

RESULTS

STLV-III was isolated from PBL of all 12 cohort animals when cocultivated on HUT-78 cells at 2 weeks PI. In addition, all 12 animals seroconverted for STLV-III structural proteins by 2 weeks PI using radioimmunoprecipitation and sodium dodecyl sulfate-polyacrylamide gel electrophoresis of STLV-III-infected HUT-78 lysates [11]. Nine of the 12 had a lymphocytosis, monocytosis, or leukopenia on at least one complete blood count during the study period.

Of the 12 STLV-III-inoculated animals, 10 (83%) developed a maculopapular, erythematous, nonexcoriated cutaneous eruption of the trunk, groin, medial thigh, and face (Fig 1). All animals given the high-dose inoculum (group 1) developed this eruption. One animal (Mm 167-84) in this group showed macular erythema at approximately 1.5 weeks PI that peaked at 3 weeks PI to include red, slightly raised papules and coalescing macules. These lesions lasted until 6.5 weeks PI. The second animal (Mm 191-84) developed a similar rash at 2.5 weeks PI that exhibited a course identical to the first animal. The other 2 in group 1 (Mm 214-84 and Mm 202-84) had only mild eruptions that began at 1.5 weeks PI, peaked at 2 weeks PI, and lasted for 1 week. Three of four macaques in both groups 2 and 3 developed mild rashes identical

Figure 1. Photograph of the groin and abdomen of a 6-month-old macaque (Mm 382-84) 3 weeks after inoculation with STLV-III. There are multiple erythematous macules (arrowhead, lower right) that have coalesced to form a confluent zone of erythema involving the abdomen (border delineated by arrowheads). The shaved right groin and abdomen also show loose debris and hair stubble.

Figure 2. Light photomicrographs of H&E stained sections of skin of macaques 3 weeks after inoculation with STLV-III. A, (Mm 191-84). There is a perivascular inflammatory infiltrate within the superficial dermis. The epidermis is mildly hyperplastic with orthokeratotic hyperkeratosis (scale bar = 80 μm). B, (Mm 167-84). The epidermal and dermal infiltrates consist predominantly of mononuclear inflammatory cells consistent with lymphocytes (scale bar = 40 μm).
an eruption occurring 4-6 weeks after presumed HTLV-III exposure and before HTLV-III antibodies were detected in the serum. No inflammation, endothelial changes, or epidermal abnormalities were detected in biopsy specimens at 12 weeks. Biopsies from control animals were normal throughout the study period.

**DISCUSSION**

Previous reports have documented a cutaneous maculopapular rash associated with HTLV-III infection in humans [5-8]. Two of these studies described a transient rash in approximately one-half [7] to two-thirds [6] of acutely infected patients who presented with mononucleosis-like symptoms. Ho et al [6] described an eruption occurring 4-6 weeks after presumed HTLV-III exposure and before HTLV-III antibodies were detected in the serum. Similarly, James et al [5] noted a chronic papular eruption much later in the course of infection in patients with AIDS-related complex (ARC) and AIDS. Three of the four patients described in the report had a superficial perivascular mononuclear infiltrate, while the fourth had a perivascular and perifollicular granulomatous dermatitis. A disseminated papular granulomatous dermatitis has also been described briefly in 2 patients with AIDS [8]. It remains uncertain whether the eruptions occurring with ARC or AIDS are related to those occurring after acute HTLV-III infection because of the paucity of skin biopsies from patients during the preclinical course of their disease. The STLV-III macaque model, therefore, provides a unique opportunity to prospectively study the earliest dermatologic manifestations of infection by this novel retrovirus.

The nature and distribution of inflammatory cells in the dermis of infected macaques is remarkably similar to the exanthem described in HTLV-III-infected individuals with ARC or AIDS [5], the exception being those patients with granulomatous dermatitis. In addition, like infection in humans, the rash in the macaque is transient, occurs within weeks after exposure to virus, and affects a large proportion of those infected [6,7].

Though nonspecific, a superficial perivascular mononuclear cell infiltrate, associated endothelial cell hypertrophy and degeneration, and presence of lymphoid cells in a slightly hyperplastic epidermis resemble the changes occurring in a delayed hypersensitivity response (DHR) [12]. In particular, the endothelial hypertrophy and degeneration observed in this study are similar to those described in experimental DHR affecting the skin [13]. Critical to the initiation of DHR are epidermal dendritic cells (Langerhans cells) that function to present cutaneous surface antigens to T cells [14]. Recently, it has been proposed that dendritic cells in the skin and lymph node may be involved in the earliest immune response to infection with HTLV-III [15]. Whether the cutaneous alterations observed in the STLV-III model herald early events in altered immunoregulation related to retroviral infection is the subject of ongoing investigation.

It is important to note that the rash was most severe and persistent in animals given the highest viral dose, while those not developing the rash received less concentrated doses. These findings suggest that the development of cutaneous lesions associated with T-cell tropic retroviral infection may be dose-dependent, although the mechanisms by which viral dose induces or prolongs this eruption are not known. Careful correlation of the incidence and severity of cutaneous lesions in these animals with evolving immunologic profiles and clinical outcome is fundamental in establishing the pathogenic and prognostic significance of this earliest manifestation of STLV-III infection in the macaque.

The recognition of this cutaneous eruption as a clinical entity associated with acute T-cell tropic retroviral infection in macaque monkeys should facilitate investigation of comparable cutaneous
manifestations associated with HTLV-III infection in humans. Mononuclear cell networks in skin and draining lymph nodes provide closely allied immunoregulatory functions [16]. Characterization of early cutaneous alterations, therefore, could be of value in elucidating the early, preclinical effects of T-cell tropic retroviral infection on human and nonhuman primate immune systems.

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REFERENCES