Intestinal Plasma Cell Alterations in Acquired Immunodeficiency Syndrome

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Immunofluorescence studies of plasma cells were performed on small intestinal and colonic biopsies obtained from a series of patients with acquired immunodeficiency syndrome or the "AIDS related complex" plus homosexual male and heterosexual controls. The AIDS group was significantly depleted of IgA plasma cells compared to the control groups. In contrast, the numbers of IgM plasma cells were increased in the AIDS and homosexual control groups compared to the heterosexuals. Plasma cell fluorescence intensities for IgA and IgM were decreased in the AIDS patients, implying less cytoplasmic immunoglobulin per cell. The frequency of IgA plasma cell depletion did not differ in men and women, patients with opportunistic infections or Kaposi's sarcoma, or in patients with and without gastrointestinal symptoms. The extent of IgA plasma cell depletion did not correlate with serum IgA concentrations. IgA plasma cell numbers also did not correlate with selected parameters of nutritional status and intestinal absorption. Studies of salivary IgA output demonstrated decreased secretion of soluble IgA in AIDS patients, and an increased secretion of IgA in particulate form. These results suggest that abnormalities in IgA secretion occur in AIDS and might influence its clinical manifestations.

The mucous membranes, including the gastrointestinal tract, share in immunoglobulin secretion, a function distinct from other lymphoid tissues in the body. Secretory immunoglobulins prevent the adherence of pathogens and other antigens to the epithelia and their entry into the body. Proper function of the secretory immune system requires the coordinated activity of epithelial cells, antigen-processing cells, several classes of T cells, and plasma cells (1). A deficiency of secretory IgA, the major secretory immunoglobulin, may be associated with recurrent intestinal, pulmonary, or sinus infections (2). Secretory IgA deficiency also may have systemic complications, possibly related to circulating immune complexes due to excess antigen absorption (3).

The acquired immunodeficiency syndrome (AIDS) is a newly described disorder of systemic immune function (4). The primary defect in AIDS is felt to be the destruction of specific subsets of helper T lymphocytes, due to infection by a retrovirus (HTLV III/LAV) (5). The immunologic derangement is widespread, including functional abnormalities of T cells (6), B cells (7), antigen-processing cells (8), and macrophages (9). The effect of acquired immunodeficiency on secretory immunity has not been described, although B lymphocyte function is modulated by T cells at many points. The development of mucous membrane infections such as candidiasis and chronic intestinal cryptosporidiosis, as well as Pneumocystis carinii pneumonia, implies that secretory immunity is impaired in patients with AIDS.
The purpose of this study was to evaluate IgA-, IgM-, and IgG-containing plasma cells in frozen biopsies using immunofluorescence techniques.

**MATERIALS AND METHODS**

**Study Groups.** Biopsies from 59 subjects were studied. Thirty-four patients had the acquired immune deficiency syndrome, according to criteria established by the Centers for Disease Control (10), and five patients were felt to have the "AIDS-related complex," with lymphadenopathy, weight loss, and recurrent oropharyngeal candidiasis, among other symptoms (Table 1). For the purposes of this report, the term AIDS will refer to subjects from both subgroups. Thirty-four of the patient's were male and five were female. Eight patients, including four of the five females were former intravenous drug users. One woman had no clear risk factor for developing the disease.

All patients had been treated for oral candidiasis. At the time of study, 31 patients had been treated for other opportunistic infections, six for Kaposi's sarcoma, and two for both complications. Twenty patients had chronic diarrhea. In 11 patients microbiologic studies failed to reveal any etiologic agent underlying the diarrhea, although several patients had evidence of active herpes simplex virus or cytomegalovirus (CMV) infection. Thirteen of the AIDS patients had been evaluated as part of a previous study (11).

Ten homosexual male controls were studied. Most were recruited from a cohort of homosexual males in New York City participating in a longitudinal study of systemic immune function (courtesy of Dr. Michael Lange). Eight subjects are alive and well after 15-23 months of follow-up and two patients were lost to follow-up. Four subjects complained of altered bowel habits at the time of study. Symptoms disappeared in three subjects and have recurred on several occasions in the fourth. In addition, 10 heterosexuksamal patients and four males were studied. They had been evaluated for gastrointestinal symptoms, but no infectious, immunological, malignant, or inflammatory lesions were found, other than a gastric ulcer in one patient. Studies of salivary IgA output were performed in 10 AIDS patients and 10 subjects from each control group. These AIDS subjects were different from those who were biopsied (Table 1). Subjects for the two control groups were recruited specifically for these studies and did not have gastrointestinal complaints. The studies were approved by the Institutional Review Board at St. Luke's-Roosevelt Institute for Health Sciences. All subjects gave informed consent before any biopsies were performed.

**Intestinal Biopsies.** Small intestinal biopsies were obtained in 36 subjects, 24 of whom had AIDS. Tissue was obtained either from the jejunum near the ligament of Treitz, using a Crosby capsule (21 subjects), or from the duodenum by endoscopic biopsy (15 subjects). Rectal biopsies were obtained from 50 subjects, of which 37 had AIDS, either during rigid sigmoidoscopy (36 subjects) or fiberoptic colonoscopy (14 subjects). Biopsies were immediately embedded in OCT compound without prior orientation, frozen on dry ice, and stored at −70°C until assay. Batches of approximately 20 biopsies were evaluated at a time. Tissue blocks were cut into 4-μm sections at −20°C. Intestinal plasma cells were evaluated by a direct immunofluorescence technique using polyclonal rabbit anti-human antibodies to the major immunoglobulin classes (Dako Laboratories, Westbury, New York) (12). Nonimmune rabbit serum conjugated with fluorescein was used as a control for nonspecific binding. Stains for IgA, IgM, and IgG, were performed on all biopsies (Figure 1). Stains for IgD and IgE were performed on 18 biopsies each. Slides were stained in the dark, and the stained sections were stored in the dark at 4°C. Under these circumstances the material was stable for at least six months, and sections could be examined repetitively without loss of fluorescence.

**Data Analysis.** The slides were coded and reviewed independently by two of the authors (D.P.K., J.V.S.), and semiquantitative estimations were made. Under normal circumstances, the numbers of IgA-containing plasma cells greatly exceed the numbers of IgM-contain-