Outbreak of Persistent, Unexplained, Generalized Lymphadenopathy With Immunological Abnormalities in Drug Addicts in Milan

Summary: Persistent unexplained lymphadenopathy (LAS) with intermittent fever, weight loss, night sweats and malaise was observed from March to October 1983 in 16 of 133 intravenous drug addicts who had been followed for at least two years in a Center for Drug Addicts Assistance in Milan, Italy. All the subjects lived in a restricted suburban area and indulged in frequent toxicomanic practices and mutual sexual intercourse. The subjects showed immunological alterations such as lymphopenia (50%), decreased T helper/T suppressor ratio (93%), both these abnormalities (43%), decreased T helper cells (75%), increased T suppressor cytotoxic cells (81%), decreased natural killer (NK) activity (77%), anergy (50%) or hypoergy (43%) to recall skin testing and elevated levels of IgG (87%). Anti-HTLV III antibodies were found in 14 of 16 (87%) patients with LAS and in 3 of 11 (27%) symptom-free drug addicts belonging to the same group. It will be important to assess in the future whether this clinical and immunological picture results in acquired immunodeficiency syndrome in an area so far untouched by this disease.

Introduction

Acquired immunodeficiency syndrome (AIDS), first recognized in 1981 in urban areas of the U.S.A., particularly in New York and California, among homosexual men (1, 2) has been shown to affect a number of different groups at risk, even in countries other than the U.S.A. (3-9). Recently, a syndrome characterized by fever, weight loss and persistent generalized lymphadenopathy has been described in the social groups at risk for AIDS and seems to represent a prodrome for this disease (10-15). Isolated cases of overt AIDS or its prodromes have recently been reported in Italy (16). In this paper we are reporting on 16 intravenous drug addicts who belong to a group of subjects indulging in frequent toxicomanic and sexual intercourse and who developed a syndrome of generalized lymphadenopathy with immune abnormalities between March and October 1983.

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Patients and Methods

One hundred and thirty-three parenteral drug addicts (109 males and 24 females aged between 18 and 35 years) on methadone maintenance at the Center for Drug Addicts Assistance of the L. Sacco General Hospital, Milan, were followed for a period of at least two years. All the subjects lived in the same suburban area of northwest Milan. Social and behavioral conditions and toxicomanic habits were substantially homogeneous. Frequent and promiscuous heterosexual and homosexual contacts within the group are reported.

The subjects received methadone every day and were controlled by complete medical examination every two months. This report concerns a clinical and immunological study of 16 male subjects aged between 21 and 35 years (12% of the overall population) with lymphadenopathy syndrome (LAS) lasting for three months or more (lymphadenopathic drug addicts: LADA). Four subjects were active homosexual men.

Eleven symptom-free male drug addicts (SFDA) aged between 20 and 34 years from the same group of subjects as those on methadone treatment as well as 12 age and sex-matched healthy controls (HC) were also studied as controls. No homosexuals were included in the two latter groups. Antibodies to herpes simplex virus (HSV-I), cytomegalovirus (CMV) and varicella-zoster virus (VZV) were measured by complement fixation. Antibody titrations were performed by a micromethod according to standard procedures (17). IgM antibodies to cytomegalovirus were assayed by ELISA (Enzygnost/Cytomegalie, Behringwerke, Scoppito, Italy). Hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), antibody to hepatitis B core antigen (anti-Hbc) and antibody to HBeAg (anti-HBe) were assayed by radioimmunoassay kits (Abbott Laboratories, North Chicago, Ill.). Antibodies anti-HTLV III were assayed by ELISA (Enzygnost/Cytomegalie, Behringwerke, Scoppito, Italy). Hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), antibody to hepatitis B core antigen (anti-Hbc) and antibody to HBeAg (anti-HBe) were tested in serum using commercial radioimmunonassay kits (Abbott Laboratories, North Chicago, Ill.). Antibodies anti-HTLV III were detected by indirect immunofluorescence on H4 cells infected with HTLV III (18). Cutaneous delayed hypersensitivity was tested with a multipuncture instrument (Multitest C.M.I., Institut Mérieux, Lyon, France) which measures the responses to seven different antigens (tuberculin, tetanus and diphtheria anatoxins, Candida, Proteus, Streptococcus and Trichophyton extracts).

The reaction was considered positive when the mean of the sum of the diameters of the skin infiltrate was ≥ 2 mm. The sum of the diameters of the positive antigen reactions (score) was also evaluated (19). The patients were considered as anergic when they were unresponsive to all the antigens, and hypoergic when they were responsive to one antigen only. The results are presented as the mean ± S.D.

Results

The 16 cases with lymphadenopathy reported systemic symptoms consisting of fever, weight loss, malaise, anorexia and fatigue. At the time of writing this report the duration of lymphadenopathy varied from eight to more than 12 months and involved in each patient cervical, axillary and inguinal lymph nodes. Hepatosplenomegaly was found in 13 of the 16 subjects. Chest X-ray did not reveal mediastinal lymphadenopathy. Lymph node biopsies were performed in 12 individuals. Reactive lymphoid hyperplasia with a prominent follicular pattern was found in 11 cases.

In one subject, measles-like multinucleated giant cells were a distinctive feature of the paracortex of the latero-cervical lymph nodes.

Numerous OKT8+ cells were observed in the germinative centres of follicles in all the cases (eight patients) in whom immunohistochemical procedures had been performed (Figure 1). Clinical and laboratory evidence of previous infections such as toxoplasmosis (4 of 16) and primary syphilis (1 of 16) was obtained in the lymphadenopathic group, while the symptom-free drug abusers were completely negative in this respect.

Figure 1: Numerous anti-OKT8-positive cells scattered in the follicle center. Immunoperoxidase ABC method with hematoxylin counterstain (× 250).

Significance was assessed by Duncan's new multiple range test (lymphocyte counts and subpopulations), the Mann Whitney U test (NK data) and the Student's t-test (Ig and anti-viral antibody titres).

For pathological diagnosis, lymph nodes were routinely processed and sections stained with hematoxylin-eosin, Giemsa and Weigert reticulum methods.

For immunohistological evaluation in selected cases (eight patients), frozen sections of lymph nodes were stained with an avidin-biotin-peroxidase procedure (ABC) using commercially available antisera directed against T lymphocyte subpopulations: OKT4, OKT8, OKT3 (Ortho Diagnostics, Raritan, N.J.).