Haematology and Blood Transfusion Vol. 29
Modern Trends in Human Leukemia VI
Edited by Neth, Gallo, Greaves, Janka

HTLV-I Antibodies Associated with Cutaneous T Cell Lymphoma in Denmark *

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A. Introduction

The first isolation and characterization of a human retrovirus was done by Gallo and co-workers from patients with aggressive cases of adult T cell leukemia/lymphoma in the United States [15, 16]. This virus, named human T cell leukemia/lymphoma virus (HTLV-I) is a T cell-tropic retrovirus [8, 9], initially found sporadically among United States cases of adult T cell leukemias and lymphomas (ATLL) with cutaneous manifestations resembling aggressive variants of mycosis fungoides. Subsequently, HTLV-I was specifically linked to adult T cell malignancies in Japan and the Caribbean [8]. A second human retrovirus, HTLV-II, which is related to but distinct from all previous HTLV-I isolates, was identified and isolated from a patient with hairy cell leukemia [12]. Recently, a third retrovirus, HTLV-III has been isolated and is a probable etiologic agent in the acquired immune deficiency syndrome (AIDS) [4–7].

In early studies, HTLV-I was identified in less than 1% of cutaneous T cell lymphoma (CTCL) patients and therefore was not considered a likely agent in these malignancies [8]. Because of several clinical similarities between CTCL and the HTLV-positive ATLL cases, we have used a more sensitive indirect ELISA microtest for HTLV antibodies [19] for the presence of HTLV antibodies in patients with CTCL.

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B. Materials and Methods

A total of 167 serum samples from 104 patients were studied. Of these, 68 patients had CTCL. There were 5 with Sézary syndrome, 4 with mycosis fungoides tumor stage (MFIII), 15 with mycosis fungoides plaque stage, diagnostic histology (MFII), 40 with mycosis fungoides plaque stage, nondiagnostic histology (MFI), and 4 with lymphomatoid papulosis. The remaining control group of 36 contained patients with skin infiltrates of non-T cell malignancies as well as cutaneous infiltrates of benign T cells.

An ELISA assay for detection of HTLV antibodies in human sera has been developed and presented in detail earlier [19]. An additional confirmatory neutralization test was used, also described earlier in detail [19]. A suppression of the ELISA value by 50% in the sample exposed to the unlabeled anti-HTLV, relative to a standard normal human serum, was considered positive, indicated by + (confirmatory result for the presence of anti-HTLV).

C. Results and Comments

Of the 68 patients with CTCL, 10 patients were found to be HTLV antibody positive although with low titers [21]. The distribution of these HTLV antibody-positive patients among the different subgroups of CTCL is given in Table 1. The data demonstrate that positive HTLV antibody sera were found in the earliest prediagnostic stage, MFI, where tumor cells are not rec-

Table 1. Number of HTLV antibody-positive sera from 68 patients with cutaneous T cell lymphoma

Diagnosis	HTLV antibody-positive
Sézary syndrome	0/5
Mycosis fungoides (tumor stage)	2/4
Mycosis fungoides (plaque stage, diagnostic histology)	0/15
Mycosis fungoides (plaque stage, nondiagnostic histology)	7/40
Lymphomatoid papulosis	1/4
Total	10/68

ognizable in the plaque lesions as well as the later stages, MFIII, where tumor cells are histologically diagnosed and skin lesions have progressed to tumor stage. Of interest, one of the four patients with lymphomatoid papulosis had positive HTLV antibody sera. (Lymphomatoid papulosis is characterized by remittent hemorrhagic papules on the skin that in 10% of cases may progress to malignancy.) Sequential studies of at least 1 year were performed on six of the patients and, to summarize, HTLV antibody status remained constant throughout this period during which three of the patients changed from relapse to remission stages. In the control group consisting of 31 non-CTCL patients and 5 CTCL family members, all but 1 were negative in the ELISA assay for HTLV-I antibody. The positive patient had Kaposi's sarcoma.

Since the discovery, isolation, and characterization of HTLV-I in the United States, a series of epidemiologic studies have identified a particular form of aggressive T cell malignancies: adult T cell leukemias/lymphomas which are closely related to HTLV-I infection in different parts of the world [1–3, 10, 11, 13, 14, 17, 18, 20, 22, 23]. Other, much less aggressive T cell lymphomas or CTCL include mycosis fungoides, Sézary syndrome, and lymphomatoid papulosis which in past studies were HTLV negative with rare exceptions [8]. However, by more sensitive serum antibody assay [19] and a careful subtyping of patients with CTCL, we have found that positive HTLV-I antibody sera are found in cases of CTCL, including the very early clinically and nonhistologically confirmed stages, at an overall rate (15%) not previously reported or generally expected. The detection of relatively low HTLV-I antibody titers in the CTCL diseases may be explained by a restricted level of virus replication, an earlier transitory infectious stage, or only partial cross-reactivity with HTLV-I proteins used in the assay, i.e., a virus closely related to, but immunologically distinct from HTLV-I may be involved. In summary, the present data suggest that exposure to HTLV-I or a related virus exists in Denmark, that an elevated frequency of low titer antibody occurs in some cases of CTCL in the early histologically nondiagnostic (plaque) stage and also in later malignant stages, and finally that the presence of antibody is independent of the clinical status of these patients, if they are in remission or relapse.

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