Human T-cell Lymphotrophic-I–associated Leukemia/Lymphoma

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Opinion statement

Human T-cell lymphotropic virus-I (HTLV-I)–related adult T-cell leukemia/lymphoma (ATL) is a model disease for proof of viral oncogenesis. HTLV-I infection is endemic in southern Japan and the Caribbean basin, and occurs sporadically in Africa, Central and South America, the Middle East, and the southeastern United States. ATL occurs in only 2% to 4% of HTLV-I–infected people [1–3]. When it does occur, it is usually aggressive and difficult to treat; most people survive for less than 1 year [1–3]. Combination chemotherapy with cytotoxic agents has yielded complete response rates of 20% to 45%, but responses usually last only a few months [3]. Recently, novel treatments, such as monoclonal antibodies directed at the interleukin-2 receptor and the combination of interferon alfa and zidovudine, have been shown to be active in the treatment of patients with ATL. A small percentage of patients achieve long-lasting remissions [2,3].

Introduction

Adult T-cell leukemia/lymphoma (ATL) was first described in 1977 by Uchiyama et al. [4], who detailed the clinical and hematologic features in 16 patients. They found that these patients had leukemic cells that were morphologically heterogeneous, with deeply indented or lobulated nuclei. They frequently had involvement of the skin, lymph nodes, liver, and spleen. The most striking feature of this group was that 13 of them were born in the same region of southern Japan, even though they eventually migrated from this region [4]. Poiesz et al. [5] isolated the retrovirus human T-cell lymphotropic virus-I (HTLV-I) from a patient initially thought to have cutaneous T-cell lymphoma, but who is now believed to have had ATL. It is now accepted that HTLV-I is the causative agent of ATL. HTLV-I also causes several other diseases, including tropical spastic paraparesis/HTLV-I–associated myelopathy, uveitis, and infective dermatitis.

In endemic regions of Japan, 6% to 37% of the population is infected with HTLV-I, as demonstrated by antibodies to the virus [6–8]. Among these HTLV-I carriers, 1.5 per 1000 men and 0.5 per 1000 women are diagnosed with ATL each year [6–8]. The overall risk is 2.5% in a carrier that lives to age 70 years [8]. In the Caribbean islands, 3% to 6% of the population is seropositive for HTLV-I, whereas less than 1% of people in low-risk areas of the United States and Europe are infected [9–12]. Seroprevalence increases with age and is more common in females. In Jamaican people older than age 70 years, 17.4% of women are HTLV-I positive, compared with 9.1% of men [10]. In Japanese people older than age 80 years, 50% of women and 30% of men are seropositive [8].
Human T-cell lymphotropic virus-I is transmitted through sexual intercourse, breast milk, shared needles among intravenous drug users, and transfusion of blood products containing infected T cells [3–5]. Transmission of HTLV-I occurs more efficiently from males to females than vice versa [13]. This explains the higher increased seroprevalence among women, especially after the age of 30 years. The rate of male-to-female transmission correlates with the duration of relationship, increased antibody titer and viral load, increased male age, and any history of sexually transmitted disease in either partner [13]. Female-to-male transmission of HTLV-I is increased in men with genital ulcers [13].

Several studies in Japan and one in Africa have shown that the rate of mother-to-child transmission ranges from 15% to 25% and is almost always transmitted through breast-feeding, although transplacental transmission can occur [14,15]. In a study of 34 children born to seropositive women in Gabon, none of the children who became infected had detectable antibodies or proviral DNA before 18 months [14]. Risk factors for mother-to-child transmission include high HTLV-I antibody titer, prolonged ruptured membranes during delivery, low socioeconomic status, and prolonged breast-feeding [15].

Transfusion of HTLV-I–contaminated blood causes seroconversion 40% to 60% of the time, at a median of 51 days after the transfusion [16]. Due to the high efficiency of infection by contaminated blood, screening of blood donors is important, even in areas of low seroprevalence. Blood products that contain white blood cells transmit the virus, but it is not transmitted by transfusion of fresh frozen plasma [16]. Screening of blood donors is the only way to prevent this route of transmission. Although screening for HTLV-I is done in Japan, the Caribbean, and the United States, it is not performed in all areas of low seroprevalence [17–21].

**Molecular Biology**

Human T-cell lymphotropic virus-I is an enveloped, single-stranded, diploid RNA retrovirus that is lymphotropic for T lymphocytes [22–24]. The method by which HTLV-I enters T cells has not been identified. Once inside the T cell, it integrates into the host DNA randomly as a provirus. The HTLV-I genome encodes three structural genes (gag, pol, and env), two regulatory genes (tax and rex, including the truncated p21rex), and the long terminal repeats. Tax is a major transforming protein in vitro and in vivo, regulating the transcription of several genes involved in cell growth and proliferation [4,25]. Another potential mechanism by which tax may transform cells is the recently described interaction of tax with the tumor suppressor gene, p16. Antibodies first develop to the core proteins encoded by gag. This is followed by antibodies to envelope proteins, and lastly to the tax-encoded regulatory protein [22,23]. In the United States and Europe, enzyme-linked immunosorbent assay (ELISA) is used as the initial screening test, and a Western blot assay is done to confirm HTLV-I infection [4]. The confirmatory Western blot also tests for reactivity to an HTLV-II envelope protein. This distinction is necessary due to the similar genome but different pathogenicity of these two viruses [4].

Despite the antibody response noted earlier, the antibodies are not effective in clearing the retrovirus from many patients. Portions of the tax protein also bind to HLA-A02 and elicit a strong cytotoxic T-lymphocyte response. Despite this, ATL has been documented in HLA-A02 patients. It appears that after infection occurs in these individuals, mutations in the tax gene occur that render the protein less immunogenic by interfering with binding to HLA-A02 [26•]. Additionally, patients with HTLV-I infection and lymphoma have been shown to have functionally deficient dendritic cells, which are important in the presentation of the viral antigen to cytotoxic T-lymphocytes [27•]. Thus, it is apparent that post-infection, selection of infected cells with genetic mutations results in the development of viros that can escape immune detection, and changes in the host immune system allow progression.

**Clinical Features/Diagnosis**

Despite the high seroprevalence of HTLV-I, less than 5% of carriers develop ATL [3–5]. The incubation period for the development of ATL is 20 to 40 years [3–5]. Therefore, HTLV-I infection early in life is likely necessary for the development of ATL. In people infected before age 20 years, the lifetime risk of developing ATL is about 5% [4]. Due to the long latency period and low incidence, it is difficult to study the progression from HTLV-I to ATL [28–34,35•]. Hisada et al. [30] evaluated several potential markers as possible predictors for progression to ATL in HTLV-I carriers. They evaluated the number of circulating abnormal lymphocytes, the level of HTLV-I titer, and the level of antibody to the Tax regulatory protein. A low prevalence of antibody to Tax had already been shown to be a feature of ATL [31]. The study, which included five cases of ATL and 38 matched HTLV-I positive controls, did not show significant differences between the two groups in any of the risk factors studied. However, the authors did discover a strong association between HTLV-I titer and progression to ATL. For every twofold increase in titer, there was a 1.6-fold increase in the risk for ATL. The study also showed that all of the patients with ATL had low or undetectable levels of antibody to Tax for up to 10 years preceding their diagnoses. The authors concluded that loss of anti-Tax antibody occurs at some point in the development of ATL [30].

Takatsuki et al. [7] evaluated the clinical features of 187 patients in Japan who had ATL. The median age of onset was 55 years. Lymphadenopathy (72%) was the most common physical finding. Hepatomegaly (47%),