Expanding Spectrum of HTLV-1-Related Diseases: Implications in Understanding the Mechanisms of Viral Pathogenesis

In addition to the well-known adult T-cell leukemia (ATL), human T-cell leukemia virus type I (HTLV-1) has been implicated in the pathogenesis of many diseases (1, 2). However, little is understood about the mechanisms of pathogenesis by HTLV-1. We have many basic and important questions that remain to be answered. Are there any subtypes of HTLV-1 that are specific to some diseases? Are there any specific mutations in the virus gene that determine the virulence? Do people with a specific genetic background develop a specific type of HTLV-1-associated disease? Regarding ATL, it is not known whether or not HTLV-1 is involved in all the steps of malignant transformation of the infected T cells. Considering the inflammatory diseases such as tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP/HAM), there is yet no real answer to the question of whether or not HTLV-1 infection of the neurological tissue is responsible for the inflammation. To answer these questions, careful description of diseases associated with HTLV-1 and understanding of the molecular biology of HTLV-1 are essential. In this context, the case report by Osato et al (3) facilitate realization of the wide variety of diseases possibly associated with HTLV-1. Yamaguchi et al previously reported epidemiological data that suggested a close correlation between HTLV-1 infection and chronic renal failure (4), to which little attention has been paid. Thus, it is of interest that the patient reported by Osato et al (3) had chronic renal failure as well as aplastic anemia and many other disorders.

The diseases that are reported to be associated with HTLV-1 can be divided into a few categories. First, the diseases that are established as a clinical entity caused by HTLV-1, such as ATL (1), TSP/HAM (5) and HTLV-1 uveitis (HU) (6). They have a firm background of epidemiological data, and unique clinical features that distinguish them from similar diseases. In this context, the T-cell alveolitis which is characterized by infiltration of T cells into the alveoli should be included in this group (7). However, the absence of clinical symptoms in most patients may be a problem shielding it from being recognized as an independent clinical entity. Secondly, there are diseases that have been shown to be associated with HTLV-1 infection but have not generally been accepted as being caused by HTLV-1. These include infectious dermatitis (8), Sjögren's syndrome (9), arthritis (10) and myositis (11). These diseases lack either epidemiological background or unique clinical features to be considered as an independent entity. Thirdly, some diseases have been suggested to be associated with HTLV-1, mostly because of seropositivity for HTLV-1, but they usually do not have a characteristic epidemiological background or unique clinical features. There are also some reports describing detection of HTLV-1 provirus sequence by PCR and negative serology in patients. Obviously, implications of these reports remain to be investigated.

Description of a new disease prompted studies on epidemiology and pathophysiology. The findings of those studies has progressed the understanding of the mechanism of HTLV-1 pathogenicity. For example, analyses of HTLV-1-infected cells in the peripheral blood of TSP/HAM patients reveals a 10- to 100-fold increase in the number of HTLV-1-infected cells, which is also observed in HU patients (12, 13). The increased viral load is now considered a basis for developing inflammatory diseases, although the mechanisms of expansion of HTLV-1-infected cells in these individuals remain to be studied. Epidemiological studies of HU patients demonstrated an extraordinarily high rate of association with Graves' disease or hyperthyroidism (14). The fact that in all the cases hyperthyroidism preceded the onset of uveitis suggested that the thyroid hormone may induce HTLV-1 gene expression. Actually, we have found that the thyroid hormone receptor alpha interact with HTLV-1 LTR and activate gene expression (15), which opened a new possibility that steroid hormones may participate in the regulation of viral gene expression in vivo. The spinal cord lesions of TSP/HAM patients are characterized by infiltration of T lymphocytes (16). In HU patients, one of the major clinical characteristics is infiltration of T lymphocytes in the affected eye, usually causing minimal tissue damage (17). These findings suggest that one of the primary abnormalities causing inflammatory diseases may reside in the abnormal homing behavior of HTLV-1-infected T lymphocytes. In fact, aberrant expressions of adhesion molecules have been documented in ATL cells and HTLV-1-infected cell lines (18–21). These results underscore the importance of discovering new diseases associated with HTLV-1 and careful description of pathobiology, which can lead to new insights into the pathogenicity of HTLV-1 as well as the mechanisms underlying disease processes. Further studies are necessary to elaborate on more effective and appropriate modalities of therapy as well as...
a means to prevent disease development.

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References