gene expression leads to neoplastic transformation; *tax* can interfere with G_1 and mitotic cell-cycle checkpoints, block apoptosis, inhibit DNA repair, and promote antigen-independent T cell proliferation. Induction of a cytokine–autocrine loop has been proposed; however, IL-2 is not the crucial cytokine. The involvement of IL-4, IL-7, and IL-15 has been proposed.

In light of the irregular expression of *tax* in ATL cells, it has been suggested that *tax* is important in the early phases of transformation but is not essential for the maintenance of the transformed state. The maintenance role is thought to be due to *hbz* expression. As is clear from the epidemiology of HTLV-1 infection, transformation of an infected cell is a rare event and may depend on heterogeneous second, third, or fourth genetic hits. No consistent chromosomal abnormalities have been described in ATL; however, aneuploidy is common and individual cases with p53 mutations and translocations involving the T cell receptor genes on chromosome 14 have been reported. *Tax* may repress certain DNA repair enzymes, permitting the accumulation of genetic damage that would normally be repaired. However, the molecular pathogenesis of HTLV-1-induced neoplasia is not fully understood.

FEATURES OF HTLV-1 INFECTION

Epidemiology HTLV-1 infection is transmitted in at least three ways: from mother to child, especially via breast milk; through sexual activity, more commonly from men to women; and through the blood—via contaminated transfusions or contaminated needles. The virus is most commonly transmitted perinatally. Compared with HIV, which can be transmitted in cell-free form, HTLV-1 is less infectious, and its transmission usually requires cell-to-cell contact.

HTLV-1 is endemic in southwestern Japan and Okinawa, where >1 million persons are infected. Antibodies to HTLV-1 are present in the serum of up to 35% of Okinawans, 10% of residents of the Japanese island of Kyushu, and <1% of persons in nonendemic regions of Japan. Despite this high prevalence of infection, only ~500 cases of ATL are diagnosed in this area each year. Clusters of infection have been noted in other areas of the Orient, such as Taiwan; in the Caribbean basin, including northeastern South America; in northwestern South America; in central and southern Africa; in Italy, Israel, Iran, and Papua New Guinea; in the Arctic; and in the southeastern part of the United States (Fig. 225e-4). An estimated 5–10 million persons have HTLV-1 infection worldwide.

Progressive spastic or ataxic myelopathy developing in an individual who is HTLV-1 positive (i.e., who has serum antibodies to HTLV-1) may be due to direct infection of the nervous system with the virus, but destruction of the pyramidal tracts appears to involve HTLV-1-infected CD4+ T cells; a similar disorder may result from infection with HIV or HTLV-2. In rare instances, patients with HAM are seronegative but have detectable antibody to HTLV-1 in cerebrospinal fluid (CSF).

The cumulative lifetime risk of developing ATL is 3% among HTLV-1-infected patients, with a threefold greater risk among men than among women; a similar cumulative risk is projected for HAM (4%), but with women more commonly affected than men. The distribution of these two diseases overlaps the distribution of HTLV-1, with >95% of affected patients showing serologic evidence of HTLV-1 infection. The latency period between infection and the emergence of disease is 20–30 years for ATL. For HAM, the median latency period is ~3.3 years (range, 4 months to 30 years). The development of ATL is rare among persons infected by blood products; however, ~20% of patients with HAM acquire HTLV-1 from contaminated blood. ATL is more common among perinatally infected individuals, whereas HAM is more common among persons infected via sexual transmission.

Associated Diseases • ***ATL*** Four clinical types of HTLV-1-induced neoplasia have been described: acute, lymphomatous, chronic, and smoldering. All of these tumors are monoclonal proliferations of CD4+ postthymic T cells with clonal proviral integrations and clonal T cell receptor gene rearrangements.

ACUTE ATL About 60% of patients who develop malignancy have classic acute ATL, which is characterized by a short clinical prodrome (~2 weeks between the first symptoms and the diagnosis) and an aggressive natural history (median survival period, 6 months). The clinical picture is dominated by rapidly progressive skin lesions, pulmonary involvement, hypercalcemia, and lymphocytosis with cells containing lobulated or "flower-shaped" nuclei (see Fig. 134-10). The malignant cells have monoclonal proviral integrations and express CD4, CD3, and CD25 (low-affinity IL-2 receptors) on their surface. Serum levels of CD25 can be used as a tumor marker. Anemia and thrombocytopenia are rare. The skin lesions may be difficult to distinguish from those in mycosis fungoides. Lytic bone lesions, which are common, do not contain tumor cells but rather are composed of osteolytic cells, usually without osteoblastic activity. Despite the leukemic picture, bone marrow involvement is patchy in most cases.

The hypercalcemia of ATL is multifactorial; the tumor cells produce osteoclast-activating factors (tumor necrosis factor α, IL-1, lymphotoxin) and can also produce a parathyroid hormone–like molecule. Affected patients have an underlying immunodeficiency that makes them susceptible to opportunistic infections similar to those seen in patients with AIDS (Chap. 226). The pathogenesis of the immunodeficiency is unclear. Pulmonary infiltrates in ATL patients reflect leukemic infiltration half the time and opportunistic infections with organisms such as *Pneumocystis* and other fungi the other half. Gastrointestinal symptoms are nearly always related to opportunistic infection. *Strongyloides stercoralis* is a gastrointestinal parasite that has a pattern of endemic distribution similar to that of HTLV-1. HTLV-1-infected persons also infected with this parasite may develop ATL more often or more rapidly than those without *Strongyloides* infections. Serum concentrations of lactate dehydrogenase and alkaline

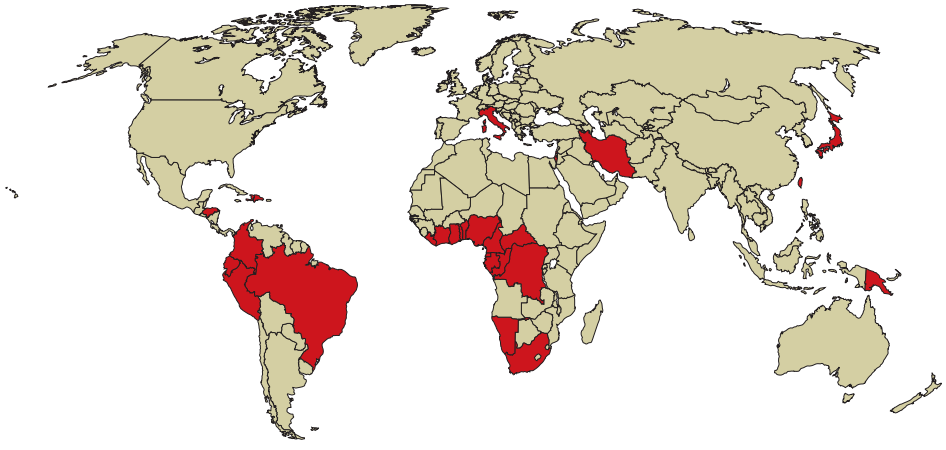

FIGURE 225e-4 Global distribution of HTLV-1 infection. Countries with a prevalence of HTLV-1 infection of 1–5% are shaded darkly. Note that the distribution of infected patients is not uniform in endemic countries. For example, the people of southwestern Japan and northeastern Brazil are more commonly affected than those in other regions of those countries.