Medical Progress

Adult T-Cell Leukemia-Lymphoma

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Adult T-cell leukemia-lymphoma, an aggressive T-cell leukemia, is characterized by the presence in the peripheral blood of malignant T cells that have highly indented or lobulated nuclei. Phenotypically the cells are usually helper T cells, but functionally they behave as suppressor cells. Patients have skin and lung involvement, hepatosplenomegaly, moderate lymphadenopathy sparing the mediastinum, and various metabolic abnormalities such as hypercalcemia. The clinical course may be chronic or acute, usually followed by a rapidly progressive terminal course. Adult T-cell leukemia-lymphoma is now known to be caused by human T-cell lymphotropic virus type I, which has been identified in the cells of patients with the disease.

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Adult T-cell leukemia or adult T-cell leukemia-lymphoma (ATLL) is an aggressive T-cell leukemia that was first described in 1977 by Uchiyama and co-workers in a group of adult patients living in southwestern Japan.[1] It is characterized by the presence in the peripheral blood of malignant helper T cells that have highly indented or lobulated nuclei. Patients present with skin and lung involvement, hepatosplenomegaly, lymphadenopathy sparing the mediastinum, and hypercalcemia. The clinical course may be chronic or acute but is usually followed by a rapidly progressive terminal course. This unusual clinical syndrome is now known to be caused by human T-cell lymphotropic virus type I (HTLV-I), which has been identified in the cells of patients with ATLL.[2,3] I will review the epidemiologic and clinicopathologic features of ATLL and will discuss the current understanding of the way in which HTLV-I transforms human T cells.

Epidemiology

One of the most striking features of the original group of patients described by Uchiyama and associates was the geographic proximity of their birthplaces.[1] All of the patients lived in or around big cities on the island of Honshu in southwestern Japan at the time of the diagnosis of ATLL; 13 of 16 had been born and had grown up on Kyushu, 8 of them in the province of Kagoshima. To explain this unusual clustering of cases, a search for an oncogenic virus was undertaken. Working independently, Gallo and colleagues[2] and Hinuma and co-workers[3] isolated a unique type C retrovirus from patients with ATLL that they called HTLV-I. Gallo's group identified viral particles in an HUT-102 T-lymphoblastoid cell line from a patient originally thought to have aggressive cutaneous T-cell lymphoma but recognized in retrospect to have ATLL. Hinuma and associates identified the same retrovirus in an MT-1 cell line from a patient with ATLL.[3]

Since identification of HTLV-I, extensive seroepidemiologic surveys have shown that the virus exists not only in Japan, where it is the most common cause of leukemia-lymphoma,[4] but also in other parts of the world. It is now known to be endemic in the Caribbean, where it is associated with half the cases of T-cell leukemia-lymphoma,[4,5] central Africa, the Pacific basin, northeastern South America, and the southeastern United States.[6-9] Cases have also been identified in nonendemic regions such as Israel and Great Britain; in many of these cases, patients had immigrated from or traveled to an endemic area.[9-11]

Serum antibodies to HTLV-I are found not only in patients with ATLL but also in lower titers in healthy adults.[6,11,12] A large epidemiologic survey in Japan showed that the antibody was present in 6% to 37% of healthy adults living in endemic regions but only sporadically among those living in nonendemic regions.[11] Healthy relatives of patients with ATLL have an especially high incidence of seropositivity.[6,13,14] In one study, almost 50% of relatives of virus-positive Japanese ATLL patients were seropositive; in the United States and the West Indies, relatives had a three to four times incidence of seropositivity compared with the general population.[15]

Epidemiologic surveys such as these indicate that the virus is not widely distributed in the general population, a finding that can be explained at least partially by the mode of transmission of HTLV-I. The virus appears to be transmitted in one of three ways, each of which requires the passage of infected cells from one person to another.[8,16,17] These include the passage of infected semen from one partner to another during sexual intercourse; the passage of infected blood cells from person to person either through a blood transfusion or intravenous drug use; and passage from mother to fetus, possibly in breast milk or through the transplacental transmission of infected lymphocytes.[8,18-21]

Etiology

Evidence Implicating HTLV-I

The human T-cell lymphotropic virus type I was implicated as the agent responsible for ATLL when in vitro studies showed incorporation of its proviral sequences into the DNA

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ABBREVIATIONS USED IN TEXT

ATLL = adult T-cell leukemia-lymphoma
HTLV-I = human T-cell lymphotropic virus type I
IL-2 = interleukin-2
LDH = lactic dehydrogenase

of host ATLL cells.[22] In addition, cocultivating HTLV-I-infected T cells and normal T cells resulted in a rapid transformation of normal cells.[10,23] The immortalized cell lines resembled primary tumor cells from ATLL patients morphologically as well as in other ways: they showed the potential for indefinite growth, had an increased number of interleukin-2 (IL-2) receptors, and showed a decreased requirement for IL-2.[4,10,14] Although the virus can infect cells other than T cells, it does not cause their transformation.[8]

Studies of patients with malignant disorders other than ATLL further support the association between HTLV-I and ATLL. A monoclonal or oligoclonal pattern of viral integration is seen in malignant ATLL cells but not in other types of malignant cells, showing that viral infection precedes expansion of the malignant ATLL clone.[8] In addition, the incidence of seropositivity among patients with other malignant tumors living in either endemic or nonendemic regions approximates that of other healthy adults in the same regions.[11,17] This suggests that the presence of anti-HTLV-I antibodies in patients with other malignant diseases is a coincidental finding.

Epidemiologic and in vitro evidence supports the concept that HTLV-I is acquired during life, rather than being inherited. First, the incidence of seropositivity increases with increasing age, reaching a maximum between ages 40 and 60[11]; the disease tends to affect older persons; and it develops in people who emigrate from endemic to nonendemic regions later in life.[9,24] Thus, infection by the virus appears to predate the emergence of malignancy. Second, HTLV-I proviral sequences are found in the DNA of neoplastic T cells but not in the DNA of nonneoplastic B cells from the same patient,[25] supporting the concept that HTLV-I is an exogenous virus acquired by infection and not by transmission in the germ line.

Despite the apparent role that HTLV-I plays in causing ATLL, infection with the virus alone apparently is not sufficient to cause the development of ATLL. It is estimated that as many as 98% to 99% of patients infected with HTLV-I never have any signs or symptoms of the disease, suggesting that another cofactor is necessary for the development of overt leukemia in infected persons.[8] The long latent period between infection and the development of disease, the variable rate of progression of the disease in infected persons, and the in vitro finding that the virus is only expressed in cells harvested from ATLL patients after they have been in culture all support the idea that a cofactor is necessary.[26] Because active infection is not required for the growth of ATLL cells, it is possible that HTLV-I is necessary for inducing leukemia but is not adequate for the maintenance and progression of the disease.[8,27]

The Virus and Mechanisms of Transformation

The mechanism by which HTLV-I causes the transformation of normal T cells is not fully understood. It is clear, however, that this virus is unique among known acute or chronic transforming retroviruses. First, it has no sequences that are homologous to known oncogenes.[28,29] In addition, it shows no preference for a specific site of integration into cellular DNA, the site varying from tumor to tumor.[30] Thus, HTLV-I does not cause a transformation of T cells by either insertional mutagenesis or viral oncogenesis.[4,29]

The structure of HTLV-I is similar to that of animal oncogenic retroviruses. It has a long terminal repeat at the 5′ and 3′ ends of the genome; a *gag* gene, which encodes the group-specific core proteins p19, p24, and p15; a *pol* gene, which encodes reverse transcriptase; and an *env* gene, which encodes envelope glycoproteins.[26,30-32] Unique to HTLV-I is a strongly conserved gene in the 3′ region, called the *x* gene, also known as *x-lor* or *tat* (transactivator gene of transcription).[28,29] The *x* gene encodes a protein of molecular weight 40,000 that is found in the nucleus of infected cells.[28] This *x* protein, when produced in even small amounts, stimulates *x* transcription and thus viral replication.[28,29,33-35] Not only is this protein essential for the efficient replication of the virus, but it also appears to be required both for the active infection of T cells and for their immortalization. It is possible that the *x* protein induces cell transformation by causing an abnormal transactivation of factors, such as interleukin-2, involved in regulating normal T-cell proliferation.[4,8,36]

Pathology

Cellular morphology in ATLL is highly variable. The most consistent feature is the presence in the peripheral blood of pleomorphic, medium to large lymphocytes with indented or polylobulated nuclei. The cytoplasm is scant, nuclear chromatin coarsely clumped, and nucleoli inconspicuous.[37-41]

Approximately 65% of patients have leukemia at the time of presentation; it will develop in essentially all of them at some time during the course of their illness.[42] At autopsy, the bone marrow is involved in 95% of patients, although the extent of involvement may be less than expected based on the peripheral blood abnormalities.[41]

Involvement of lymph nodes, except those in the mediastinum, is common in these patients; hence, the name adult T-cell leukemia-lymphoma. Because of notable pleomorphism in the pattern of involvement of nodes,[41] however, a biopsy may not be diagnostic; examining the peripheral blood is usually more productive. This heterogeneity may hinder categorizing the nodes according to lymphoma classification systems now in use. The lymphoma is usually classified as being one of the following: pleomorphic, large-cell immunoblastic, lymphoma of medium-sized cells, or lymphoma of mixed-cell type.[37,38]

A biopsy specimen of the skin in ATLL reveals dermal and subcutaneous infiltration by tumor cells; about two thirds of patients have focal epidermal infiltration by tumor cells that may resemble Pautrier's microabscesses seen in the Sézary syndrome.[37,39,42]

At autopsy, organs other than the bone marrow, skin, and lymph nodes are often involved. Hanaoka and colleagues found malignant cells in the adrenal gland in 90% of patients, in the lung in 70%, in the liver in 56%, in the kidney in 47%, in the gastrointestinal tract in 47%, and in the central nervous system in 25%.[41] Many organs also showed calcium deposition. Pulmonary lesions were especially prominent and were often the cause of death; these lesions included infiltration by tumor cells, interstitial pneumonia, bronchopneumonia, hemorrhage, strong exudation with hyaline membrane formation, or infection with opportunistic organisms such as

Pneumocystis carinii, cytomegalovirus, herpesvirus, *Nocardia, Candida,* and *Aspergillus.*

Chromosomes and Immunology

A variety of clonal chromosome abnormalities has been found in ATLL, but no single abnormality has been consistently associated with the disease. Among those described are trisomy 7 or 7q, 14q+, +3, 6q−, 5q−, 9q−, and loss of the X chromosome.[43-46] The meaning of the cytogenetic abnormalities in ATLL is unclear because viral integration into the cellular genome occurs randomly on different chromosomes in ATLL cells from different patients.[30] Despite this, the extent of chromosomal abnormalities appears to be related to the severity of disease; many abnormalities are seen in patients with acute disease, while few if any changes are seen in patients with chronic or smoldering disease,[47] implying that cytogenetic abnormalities may evolve as the disease progresses.

Immunologic Findings

The typical surface phenotype of ATLL cells is that of mature helper T cells: CD2+, CD3+, CD4+, CD8−, and CD25+.[36,46,48] CD25, which identifies the IL-2 receptor (Tac antigen), is five to ten times as high in ATLL cells as it is in normal activated T cells.[49] Despite their helper phenotype, these cells act as suppressor cells, inhibiting normal B-cell differentiation.[48] Variants of ATLL showing a suppressor phenotype have been described; cells from these patients, who differ from typical ATLL patients in having an extremely high lactic dehydrogenase (LDH) level, may have undergone phenotypic changes during the course of the disease due to an extremely high proliferative rate, thus resulting in the loss of some original surface markers.[48]

Clinical Features

Adult T-cell leukemia-lymphoma is a heterogeneous clinical disorder that can be divided broadly into four stages based on the extent of disease and the temporal course. These include preleukemia, smoldering ATLL, chronic ATLL, and prototypical subacute or acute ATLL.[8,22,50]

In the earliest or preleukemic stage of ATLL, patients have anti-HTLV-I antibodies but are asymptomatic. The diagnosis is made when examination of the peripheral blood in patients incidentally noted to have leukocytosis reveals the presence of typical morphologically abnormal lymphocytes. Disease is detectable in the bone marrow but in no other organs. About 50% of these patients have a long-lasting spontaneous regression of their disease occurring within months to years after the original diagnosis. The other half has persistence of the T lymphocytosis; some of them will progress to the acute (crisis) phase, which is rapidly fatal despite therapy.

A second group of patients has smoldering ATLL. This group was first recognized by Yamaguchi and co-workers, who described five seropositive patients living in endemic areas who differed from typical ATLL patients in that they presented with the gradual onset of skin lesions that flared up after years.[51] The duration of disease ranged from 22 to 156 months. Skin lesions variably consisted of erythema or papules or nodules associated with slight infiltration of the skin by ATLL cells. Other than the skin findings, the physical examination showed no abnormalities. The peripheral blood of these patients showed 0% to 2% ATLL cells, and the bone marrow showed only minimal involvement; the results of blood chemistry tests were normal. Two of five patients died despite therapy when their disease transformed to a more aggressive form resembling acute ATLL; this occurred in one patient 5 years after diagnosis and, in the other, 15 years after diagnosis.

Closely related to patients with smoldering ATLL is a third group with chronic ATLL.[50] These patients are distinguished from those having smoldering ATLL by the presence of a significant number of abnormal cells circulating in the peripheral blood. They, too, may progress after months to a more acute form of the disease that is fatal.

A fourth group of ATLL patients has a prototypical subacute or acute ATLL.[1,12,37,41,52-54] These patients frequently present with rapidly progressive skin lesions variably consisting of localized or generalized erythroderma, nodules, nonspecific plaques, papules, or patches. On physical examination, about 80% of patients have mild to moderate peripheral lymphadenopathy and about half have hepatosplenomegaly. Hilar and retroperitoneal nodes are involved in as much as 50% of cases, but, in contrast to other aggressive T-cell malignant diseases, mediastinal nodes are not involved. Involvement of the lung and leptomeninges is also typical. On laboratory examination, there is usually mild anemia, a leukocyte count that may range from 10 to several hundred $\times 10^9$ per liter,[51] hypercalcemia, an elevated LDH level, an increased alkaline phosphatase concentration, and hyperbilirubinemia.[37,51,53] Patients with typical ATLL may initially respond well to chemotherapy but generally relapse rapidly with resistant disease (see discussion of treatment).

Special Complications

In contrast to other types of non-Hodgkin's lymphoma in which hypercalcemia affects about 2% of patients,[55] hypercalcemia is a prominent complication of ATLL, estimated to occur in 26% to 100% of patients at some time in the course of their illness.[56] Symptoms of hypercalcemia may actually predate the diagnosis of ATLL by several months.[54] Abnormalities of calcium metabolism may exist even in normocalcemic patients.[56]

Patients present with typical symptoms of hypercalcemia, such as lethargy, constipation, confusion, dehydration, and polyuria.[37,54-57] The hypercalcemia may be unresponsive to treatment with standard measures until chemotherapy for ATLL is instituted. Not infrequently, hypercalcemia is associated with the terminal phase of the disease and may be a cause of early death.

The mechanism of hypercalcemia in ATLL is unclear. Laboratory studies in these patients show increased bone turnover and osteoclast activation, suggesting that ATLL cells produce a humoral factor that causes increased bone resorption. This factor has yet to be identified, but possibilities under investigation include a substance with osteoclast-activating factorlike activity,[54,55,57] transforming growth factor-β,[58] a parathyroid hormonelike substance,[52,54,56] and interleukin-1.[36]

Diagnosis

The diagnosis of ATLL should be suspected in adult patients with typical clinical features and circulating neoplastic cells with pleomorphic nuclear indentations or lobulations; confirmation requires the finding that the malignant cells have a mature helper T-cell phenotype and that anti-HTLV-I

antibodies or HTLV-I proviral DNA sequences are present.[22] Although most patients will be seropositive, it may be necessary in some patients to apply newer, more sensitive techniques, such as the polymerase chain reaction, to detect HTLV-I sequences.[59]

The major disorders that must be differentiated from ATLL include chronic lymphocytic leukemia, Sézary syndrome or mycosis fungoides, non-Hodgkin's lymphoma, and Hodgkin's disease.[59] These disorders can usually be ruled out on the basis of differences in their presenting features and clinical course, a lack of typical peripheral blood malignant cells, the absence of HTLV-I, differences in immunologic markers, and a lack of typical T-β-chain gene rearrangements.[60-62] The presence or absence of hypercalcemia, an elevated LDH level, or both may be helpful but not diagnostic.

Treatment and Outcome

The treatment of ATLL depends on the extent of the disease in a particular patient. In general, patients with preleukemic, smoldering, or chronic forms of ATLL need no treatment unless they progress to a more aggressive stage.[8] In contrast, patients who have subacute or acute forms should be treated immediately with aggressive chemotherapy or radiotherapy (or both). Various regimens have been tried.[1,5,6,37,52,54,63-65] Most patients respond rapidly to aggressive therapy, but remissions are short-lived. Patients relapse either in the area of the initial disease or elsewhere, such as the leptomeninges, within months. Salvage chemotherapy may be effective briefly, but, again, patients ultimately relapse and die of resistant disease. Mortality is about 50% in less than five months.[51] Treatment is made more difficult in these patients because of the frequent presence of metabolic abnormalities such as hypercalcemia and the high rate of infection with opportunistic infections.

Because of the generally dismal prognosis of patients with acute ATLL, several experimental approaches are under investigation. Some of these include using anti-Tac monoclonal antibodies to eliminate the IL-2 receptor-expressing cells[4]; using α-emitting isotopes or toxins conjugated to anti-Tac; and using azidothymidine or 2,3-dideoxycytidine to inhibit HTLV-I infectivity and replication.[15] These approaches and others need further evaluation to determine their usefulness in ATLL.

The ATLL patients with the worst prognosis appear to be those with the highest tumor burden, hypercalcemia, opportunistic infections, and spread to the leptomeninges.[37,52,66] A recent study showed that a poor performance status and high LDH values were the most reliable independent predictors of poor response and survival[67]; high LDH levels were also associated with worse disease-free survival. A specific pathologic subclassification was not an independent predictor of a poor prognosis. Two other recent studies[36,68] have shown that serum levels of soluble IL-2 receptors correlate with tumor burden and disease activity and may in the future be used to predict prognosis.

Summary

Adult T-cell leukemia-lymphoma is a heterogeneous disorder caused by the human T-cell lymphotropic virus type I and characterized by the presence of morphologically distinct pleomorphic helper T cells circulating in the peripheral blood. Since its first description in a group of Japanese patients, our understanding both of ATLL as a discrete disorder and of the ways in which viruses may be involved in causing malignancy has expanded tremendously. With the introduction of ever-evolving sophisticated molecular techniques, it is likely that in the not-too-distant future we will understand how HTLV-I causes ATLL and will be able to apply that knowledge to the study of other cancers.

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