immunoblastic non-Hodgkin's lymphoma associated with Epstein–Barr virus (EBV).[15,16] In our patient, the expression of latent infection membrane protein 1 (LMP1), EBV nuclear antigen 2 (EBNA2) and EBV encoded small RNA (EBER) in tumor cells confirmed a type III latency of EBV infection, analogous to that found in EBV-associated lymphoproliferative disorders in immunosuppressed patients, such as those having received organ transplantation.[17,18] HTLV-I can induce immunodeficiency before the overt development of ATLL. The HTLV-I infection led to suppression of the immune system and the development of EBV-associated PCNSL.

To our knowledge, there is no existing case report on the clinicopathological features of EBV-associated PCNSL arising from patients with ATLL.

CASE REPORT

A 56-year-old Japanese man was originally hospitalized with a 3-month history of irregularly shaped, indurated erythematous plaques and nodules with central necrosis on the trunk and axillaries (Fig. 1a), without lymphadenopathy or hepatosplenomegaly. Hematological examination revealed no atypical lymphocytes. Serum lactate dehydrogenase (LDH) and calcium levels were normal. Soluble interleukin-2 receptor (sIL-2R) level was 1950 U/mL (normal range, 220–530). Serum anti-HTLV-I antibody titer was 11.9 (+) (chemiluminescent enzyme immunoassay method; normal, <1.0). Skin biopsy showed a dense infiltration of atypical lymphoid cells in the upper dermis with exocytosis of atypical cells into the epidermis (Fig. 1b). These atypical cells were characterized immunohistochemically as $CD3^+/CD4^+$, $CD8^-/CD20^-/CD56^-$. Southern blotting of biopsy-obtained DNA and hybridization with a HTLV-I-specific probe showed clonal integration of HTLV-I provirus. Further examination confirmed that the disease was limited to the skin. The patient was diagnosed as having smoldering-type ATLL (according to the Japanese Lymphoma Study Group[6]) or cutaneous-type ATLL (according to Amano *et al.*[8]). Immunotherapy was administrated, leading to a partial regression of the skin lesions. New cutaneous lesions appeared on the trunk and extremities, however, spontaneous regression of cutaneous lesions occurred partially. Immunotherapy continued and a stable condition was maintained for as long as 2 years. The serum of sIL-2R was gradually elevated but a ^{18}F-fluorodeoxyglucose positron emission tomography scan showed no evidence of extranodal sites of involvement excluding the skin.

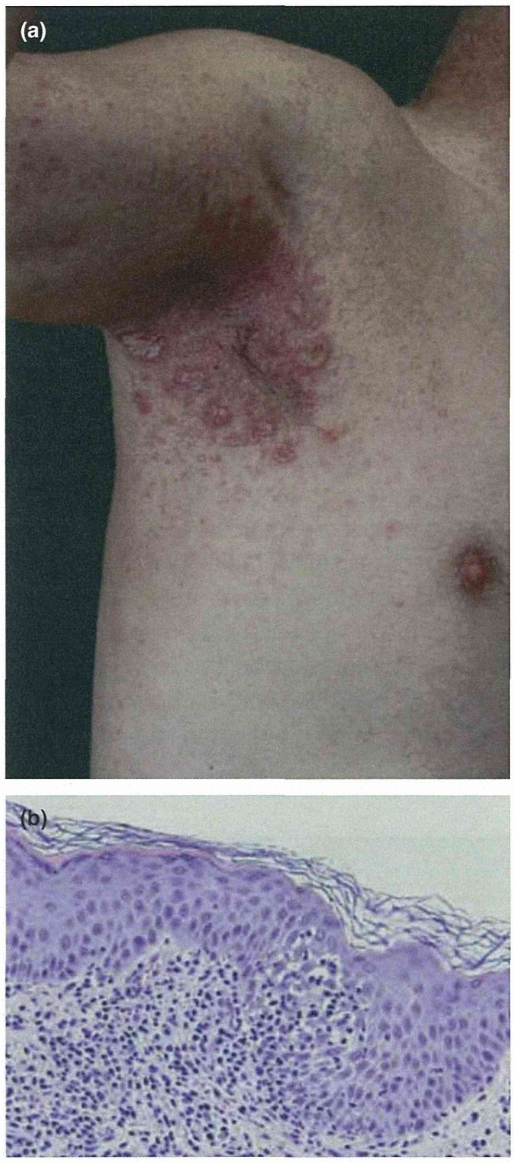

Figure 1. (a) Indurated erythematous plaques and nodules with central necrosis were observed on the trunk and axillaries on the first admission. (b) Photomicrograph showing a dense infiltration of atypical lymphocytes in the upper dermis with extension of the atypical cells into the epidermis (hematoxylin–eosin, original magnification ×10).

Two years after discharge, he was admitted with impaired consciousness, right hemiparesis and

dysarthria following a 10-day history of general malaise and a 2-day history of anorexia. On examination he appeared drowsy and disoriented (Japan Coma scale 3). The peripheral white blood cell count was 14 800/μL, no abnormal lymphoid cell was observed and the LDH was 266 IU/L (normal range, 119–229 IU/L). The serum level of sIL-2R was 9.940 U/mL. A computed tomography (CT) brain scan at admission showed two large tumors (3 cm diameter), accompanied by peritumoral edema involving the right frontal lobe and the left parietal lobe. In both tumors, hyperintense areas were observed with slight enhancement after a contrast injection. A magnetic resonance imaging (MRI) study was performed on the next day. These lesions were enhanced inhomogenously on a T_1-weighted contrast-enhanced MRI scan (Fig. 2). In view of the raised intracranial pressure, a lumbar puncture was not attempted. A stereotactic biopsy of the lesion of the right frontal lobe revealed angiocentric infiltration by large-sized atypical lymphoid cells with areas of necrosis and hemorrhage (Fig. 3a). Immunohistochemistry indicated these cells were positive for CD20, CD79a, LMP1 and EBNA2 (Fig. 3b,c) and negative for CD3, CD4, CD8, granzyme B- and T-cell restricted intracellular antigen-1 (TIA-1). A Nuclear signal was detected in the CNS lymphoma cells using *in situ* hybridization for EBER (Fig. 3d). The histological diagnosis was diffuse large B-cell CNS lymphoma. In our patient, the expression of LMP1, EBNA2 and EBER in tumor cells confirmed type III latency of EBV infection. The HTLV-I infection led to suppression of the immune system and the development of EBV-associated PCNSL. He was treated with high-dose methotrexate (MTX) (3.5 g/m^2) but continued to deteriorate and died following pancytopenia and multiple brain infarctions 2 months after the onset of his illness.

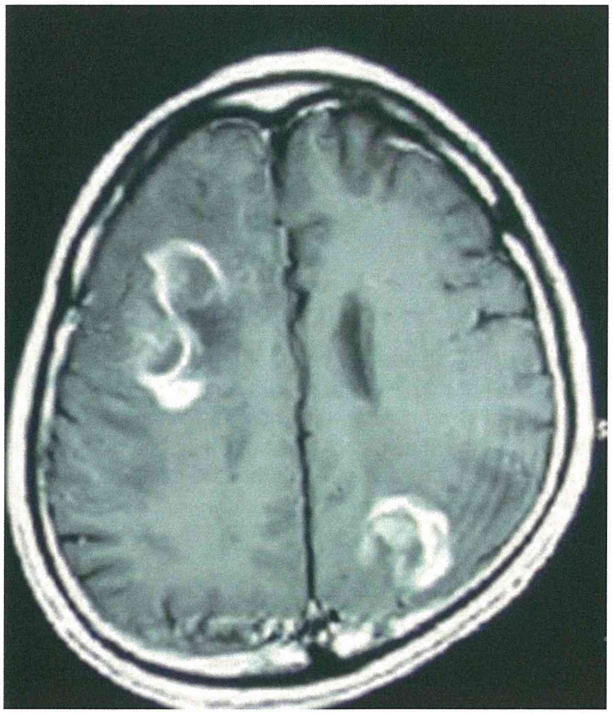

Figure 2. T_1-weighted contrast-enhanced magnetic resonance imaging scan shows high-signal foci in the right frontal lobe and the left parietal lobe.

DISCUSSION

To our knowledge, EBV-associated PCNSL has not previously been reported in ATLL. Tokunaga *et al.*[19] revealed that EBV was present within tumor cells in approximately 17% of cases with ATLL and expressed EBV oncoprotein in the tumor cells. On the other hand, Ohtsubo *et al.*[20] demonstrated that HTLV-I infected T cells and primary ATLL cells express EBV receptor/CD21 on the cell surface; however, no EBV genome was detected in either T-cell lines or primary ATLL cells. EBV-associated Hodgkin's disease has been reported in a HTLV-I seropositive patient and ATLL patients.[21,22] Tobinai *et al.*[23] reported that the immunodeficient state in patients with ATLL allows the emergence of EBV-related diffuse large B-cell lymphoma.

Epstein–Barr virus is secreted in the saliva and human infection occurs through oral transmission.[24] Oropharyngeal infection results in a lytic (productive) infection followed by the infection of circulating B cells, leading to persistence of viral DNA as an episome in the nucleus, thus establishing latent infection.[25,26] In latent infection, EBV-encoded genes, which include six nuclear antigens (EBNA-1, -2, -3A, -3B, -3C and -LP), three latent membrane proteins (LMP-1, -2A and -2B), two small non-coding RNA (EBER1 and EBER2) and *Bam*HI-A rightward transcripts, maintain the existence of the viral genome and enable it to evade immune surveillance.[27,28] In our patient, the expression of LMP1, EBNA2 and EBER in tumor cells confirmed a type III latency of

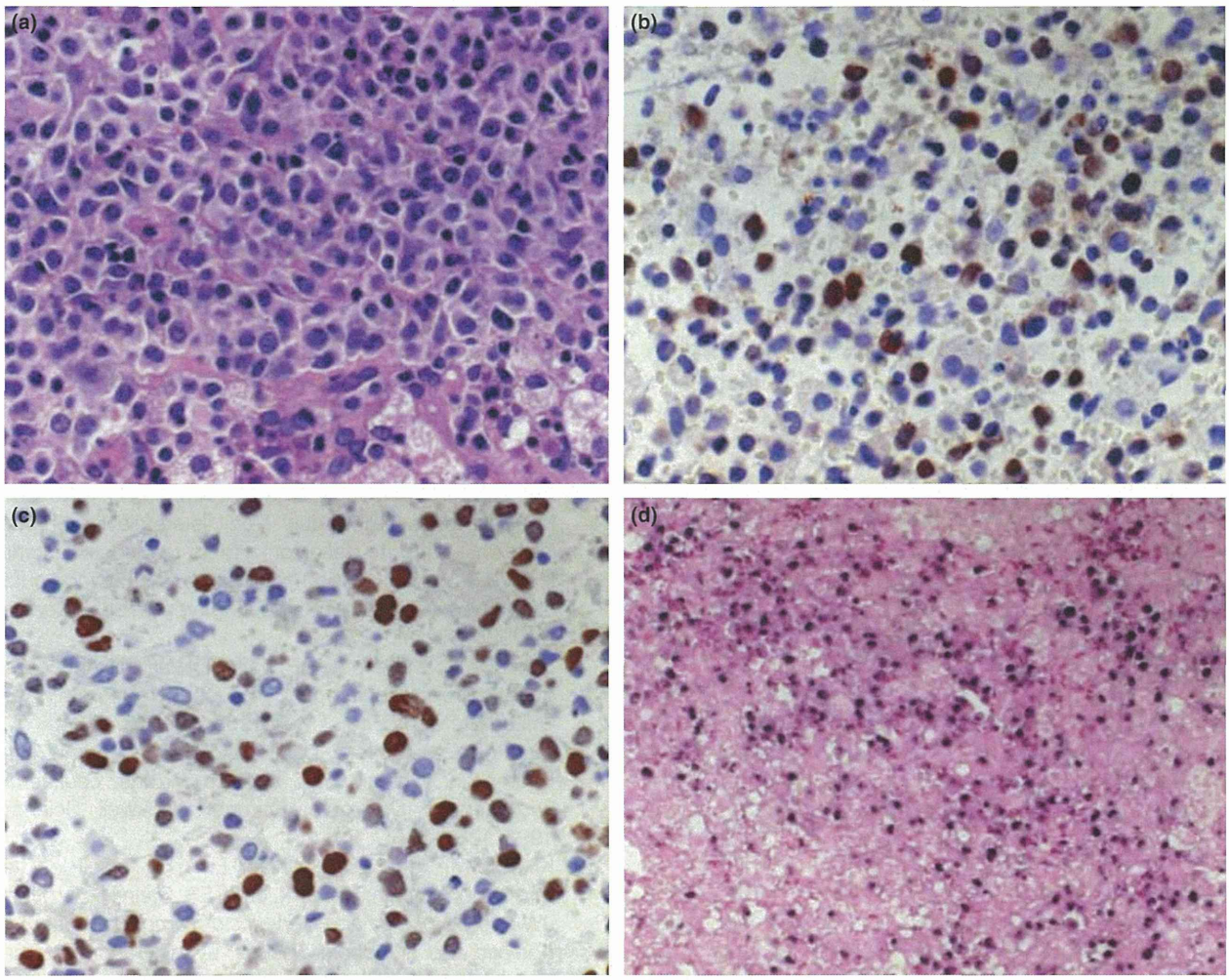

Figure 3. (a) A brain biopsy specimen showing diffuse infiltration of large atypical lymphoid cells (hematoxylin–eosin, original magnification ×40). Immunohistochemistry showing atypical lymphoid cells as positive for (b) latent infection membrane protein 1 (LMP1) and (c) Epstein–Barr virus nuclear antigen 2 (EBNA2). (d) Nuclear signal detected in central nervous system lymphoma cells using *in situ* hybridization for Epstein–Barr virus-encoded RNA (EBER) (original magnification ×20).

EBV infection, analogous to that in EBV-associated lymphoproliferative disorders in immunosuppressed patients, such as those who have received organ transplantation.[17,18] The population at risk for immune deficiency-related EBV-associated PCNSL includes a growing number of solid-organ transplant patients treated with iatrogenic immune suppression and HIV-positive patients with AIDS.[29,30] EBV-associated PCNSL has an incidence of 2–6% in AIDS patients and 1–7% in transplant recipients.[29] In the EBNA2-positive cases, the pattern of EBV-latent protein expression is identical to that observed in the majority of immunodeficiency-associated lymphomas.[31,32] HTLV-I can induce immunodeficiency before the overt development of ATLL.

Central nervous system invasion by ATLL may occur during rapid systemic progression of the disease, and its frequency is estimated at 10–25%.[33–36] Teshima *et al.*[34] reported that CNS invasion was frequently observed in the lymphoma type, but acute and chronic types predominated in a report by Kawasaki *et al.*[35] Kitajima *et al.*[37] reported that more than half the patients (12/18, 66.7%) with CNS invasion by ATLL were of the lymphoma type. The histological characteristic of primary CNS lymphoma is that of densely packed neoplastic cells which tend to cluster

along vascular channels. This supports the theory that CNS lymphoma spreads diffusely through the brain by way of the perivascular (Virchow–Robin) spaces.[38] A histological report by Taguchi *et al.*[39] described prominent infiltration of the meninges and perivascular spaces by ATLL cells. Teshima *et al.*[34] reported that the predominant site of CNS involvement in ATLL is leptomeningeal. Characteristic CT scan findings are said to be similar to PCNSL.[40]

Over 90% of PCNSL patients have histopathologically diffuse large cell lymphoma, with the majority originating from B cells.[41] Treatment of primary CNS lymphoma has not yet been standardized. Surgical resection is not recommended because it does not improve the outcome of the disease.[42] CHOP, the first-line chemotherapy for non-Hodgkin's lymphoma, was also ineffective. The low efficacy of CHOP may be because primary CNS lymphoma may be intrinsically resistant to these agents, or because cyclophosphamide, vincristine and adriamycin in the CHOP regimen do not penetrate the intact blood–brain barrier.[43] Whole-brain radiotherapy at doses over 40 Gy successfully induced 50–70% initial response rates, but the effectiveness was not durable and most of the patients relapsed and even resulted in post-radiation encephalopathy among long-term survivors.[42] Because MTX pass through the blood–brain barrier theoretically, high-dose MTX (>1 g/m^2) has been evaluated for treating CNS lymphoma. The initial response rate of high-dose MTX-based chemotherapy was 50–70%, with a median survival of 25–35 months.[42] Our patient was treated with high-dose MTX (3.5 g/m^2) but he died following pancytopenia and multiple brain infarctions. A report on AIDS-related PCNSL suggested that high-dose MTX regimens may be tolerated well and are associated with positive radiographic responses.[44]

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Review

Human T-lymphotropic Virus 1 (HTLV-1) infection – dermatological implications

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Abstract

Human T-lymphotropic virus type 1 (HTLV-1) is a type C retrovirus primarily endemic to Japan, Central and South America, the Middle East, regions of Africa, and the Caribbean. Currently, an estimated 10–20 million people worldwide are infected with this virus. Although the majority of infected individuals remain asymptomatic, HTLV-1 is the causative agent of a number of disorders, notably adult T-cell leukemia/lymphoma (ATLL) and a progressive demyelinating neurological disorder, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). In addition to ATLL and HAM/TSP, HTLV-1 has been associated with a spectrum of skin disorders, such as infective dermatitis associated with HTLV-1, crusted scabies, and leprosy. The understanding of the interaction between virus and host response has improved markedly, but there are still few treatment options.

Introduction

In 1980, the human T-lymphotropic virus type 1 (HTLV-1) was isolated from a patient with a T-cell malignancy.[1] At the present time, it is estimated that 10–20 million people worldwide are infected with HTLV-1.[2] The majority of infected people, however, remain asymptomatic. The virus can nevertheless be associated with exceptionally severe disease, such as adult T-cell leukemia/lymphoma (ATLL) and an inflammatory disease of the CNS called HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Progression to either ATLL or HAM/TSP depends upon the host immune response to the infection.[3,4] Low viral protein expression results in induction of a weak immune response, allowing the virus to persist. The virus can then induce a clonal cellular expansion, which results in ATLL.[5] Conversely, high viral load induces a vigorous immune response that has the potential to harm host tissues, resulting in HAM/TSP.[6]

HTLV-1 is a type C virus belonging to the family of Retroviridae and classified into the genus of Deltaretrovirus. The major target of HTLV-1 is the CD4+ lymphocytes; however, up to 28% of provirus can also be found in CD8+ lymphocytes.[7,8] Furthermore, Setoyama *et al.*[9] demonstrated that HTLV-I can infect cells of the sweat glands. By contrast to the human immunodeficiency virus (HIV), HTLV-1 predominantly exists as a cell-associated provirus and is transmitted as such.[10] Naturally infected T-cells hardly produce any virus, and the plasma viral load is, therefore, undetectable. However, the virus particle-associated RNA can infect new cells through a viral synapse.[11] HTLV-1 can be transmitted from mother to child through breastfeeding. HTLV-1 is also present in genital secretions of infected patients and can therefore be transmitted through sexual intercourse.[12] Transfusion of contaminated cellular blood components results in seroconversion in more than 40% of recipients.[13] As a consequence, in many countries, candidate blood donors are screened for HTLV-1 antibodies.

Laboratory diagnosis of HTLV-1 infection

Serological screening for the presence of HTLV antibodies can either be done by an enzyme immunoassay or a particle agglutination test. There are several serology-based confirmation tests, including homebrew indirect immunofluorescence assays, and commercially available Western blot and line immunoassays. Polymerase chain reaction (PCR) can provide the definite diagnosis of infection. In PCR and real-time PCR assays, proviral HTLV-1 DNA is amplified to a detectable level. Real-time PCR has the advantage that the provirus can be quantified. The provirus load is expressed as the number of HTLV-1 DNA copies per fixed number of peripheral blood mononuclear

cells. It is the most frequently used marker for prognosis and disease progression in infected patients.[14]

HTLV-1-associated cutaneous disease

Most people infected with HTLV-1 remain asymptomatic throughout life. How many people eventually develop any of the associated diseases depends on several factors, including the age of the patient and the route of infection.[15] Among HTLV-1 carriers, the lifetime risk of developing HAM/TSP ranges between 0.3 and 4%.[16] The risk of ATLL has been calculated at 1–5%.[17] Verdonck *et al.*[14] proposed to group the associated diseases into three categories: inflammatory diseases, malignant diseases, and infectious complications (Table 1). The frequency of skin lesions in HTLV-1 carriers is unknown, although sporadic cases have been reported.[18] Additionally, some reports suggest that HTLV-1-infected subjects with skin lesions such as infective dermatitis associated with HTLV-1 (IDH) have a higher risk of developing ATLL or HAM/TSP than do those without skin lesions.[19,20]

HAM/TSP

HAM/TSP is a severe and incapacitating myelopathy, more common among females.[21] Dermatological findings in patients diagnosed with HAM/TSP were compared with dermatological findings in a control group. Only xerosis, cutaneous candidiasis, and palmar erythema were significantly associated with HAM/TSP.[22]

ATLL

ATLL was first described as a new type of leukemia by Takatsuki *et al.*[23] and is caused by HTLV-1. It is endemic in southwest Japan and the Caribbean basin.[24] There are several subtypes of HTLV-1-induced ATLL; acute, lymphoma, chronic, and smoldering (Table 2).[25] Chronic and smoldering type ATLL have a relatively good prognosis, even without treatment. These types can, however, evolve to acute type ATLL, which has a poor prognosis: the median survival time (MST) after ATLL diagnosis is only six months.[26] The clonality of T-cells with HTLV-1 proviral DNA integration changes from undetectable to polyclonal and then further to monoclonal upon malignant transformation. On the basis of findings related to changes in peripheral blood, the clinical stage is considered to gradually progress from carrier to smoldering, then to chronic, and finally to acute-type leukemia.[25]

Specific skin lesions are caused by infiltration of the skin by the tumor cells and have been described in 43–72% of patients with ATLL[27] (Fig. 1). Non-specific skin lesions reported in patients with ATLL include crusted scabies and IDH.[19,28] Cutaneous lesions, both specific and non-specific, have been reported in all subtypes of ATLL. It has been suggested that mycosis fungoides (MF) might be secondary to an ongoing viral infection. HTLV-1 defective genomes were found to be present in peripheral blood mononucleal cells and cutaneous lesions of patients with MF.[29,30] However, several groups failed to detect tax-like sequences in patients with MF from USA.[31,32] Moreover, recent molecular biological studies of a diffuse population of patients with cutaneous T-cell lymphoma (CTCL) failed to detect HTLV-1 genetic sequences in lesional DNA.[33,34] These results strongly suggest that the HTLV-1 retrovirus is not involved in the pathogenesis of CTCL. Differentiation from

Table 1 HTLV-1-associated cutaneous disease

Inflammatory diseases
HAM/TSP
IDH
Sjögren's syndrome
Idiopathic polymyositis
Malignant disease
ATLL
Infectious complications
Crusted scabies
Leprosy
Strongyloidiasis

Adapted from Ref. 14.
HAM/TSP, HTLV-1-associated myelopathy/tropical spastic paraparesis; ATLL, adult T-cell leukemia/lymphoma; IDH, infective dermatitis associated with HTLV-1.

Table 2 Clinical subtypes of ATLL

Acute
Leukemic picture, organomegaly, high lactate dehydrogenase (LDH) and often hypercalcemia
Lymphoma
Organomegaly
Less than 1% circulating leukemic cells
High LDH and possible hypercalcemia
Chronic
Lymphocytosis >4 × 10^9/l with ATLL cells, skin, lung, liver or node involvement
Calcium levels normal, LDH normal or less than twice the upper normal limit
Smoldering
Skin and/or lung infiltrates (if abnormal lymphocyte < 5%, histological confirmation of lymphoma is required)
No other organ involvement
Normal lymphocyte count (≥5% ATLL cells), normal calcium and LDH normal or <1.5 the upper limit of normal

Adapted from Ref. 25.

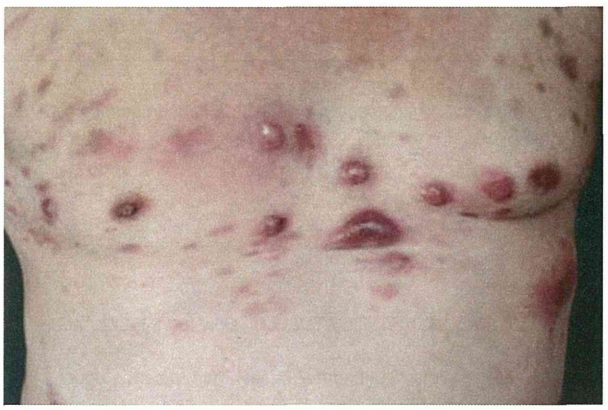

Figure 1 Cutaneous manifestation in ATLL. Multiple indurated erythema and nodules on the chest

other CTCL may nevertheless be difficult and requires demonstration of HTLV-I antibodies and the presence of HTLV-I DNA clonally integrated into the cellular DNA of neoplastic T-cells.

We previously studied 124 cases of ATLL with specific skin manifestations. The MST of smoldering-type ATLL was 16 months. We found that the smoldering-type ATLL with skin manifestations may have a worse prognosis than that without skin manifestations[35] and proposed a fifth category; namely, cutaneous type ATLL.[36] Bittencourt *et al.*[37] reported that in 52 cases of ATLL with skin involvement who were divided into primary cutaneous and secondary cutaneous ATLL, the primary cutaneous ATLL had a longer MST than the secondary cutaneous ATLL. Furthermore, the two forms of primary cutaneous ATLL, namely primary cutaneous smoldering and primary cutaneous tumoral (PCT), had different prognoses. PCT type had a shorter survival and histological characteristics, suggestive of worse outcome. Ohshima[38] analyzed the cutaneous lesions with HTLV-I proviral DNA among patients with ATLL and reported that patients with papules and tumors tend to have poorer prognosis than those with erythema. Ishida *et al.*[39] showed that tumor cells obtained from a large majority of patients with ATLL express chemokine receptor 4 (CCR4) and that the extent of CCR4 expression is significantly associated with skin involvement and poor prognosis.

In acute ATLL and occasionally in the chronic and smoldering types of ATLL, lymphocytes showing markedly hyperlobulated nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and basophilic cytoplasm, referred to as flower cells, may appear in peripheral blood.[25] During the leukemic phase, the white blood cell count may increase to hundreds of thousands. Hypercalcemia is an important complication and occurs in up to 70% of patients, often accompanied by lytic bone lesions.[40] Patients with ATLL are frequently immunocompromised, and opportunistic infections such as *Pneumocystis carinii* pneumonia, Cryptococcus meningitis, and disseminated herpes zoster are, therefore, commonly reported.[41]

ATLL is usually refractory to chemotherapy and radiotherapy. Many strategies have been evaluated for the treatment of ATLL, and several regimens do appear to improve the prognosis compared with conventional chemotherapy. These regimes include interferon-α with zidovudine, intensive chemotherapy, and allogenic hematopoietic stem cell transplantation.[40,42] Nevertheless, the median survival of patients with acute, lymphomatous, and progressing chronic ATLL has remained low, being less than one year in most reports.[26,40]

Inflammatory diseases

IDH

IDH was described in Jamaica long before the discovery of HTLV-I. Interestingly, there are markedly fewer reports of this disease from Japan than from other HTLV-I endemic regions. The Caribbean basin and, more recently, Brazil appear to be focuses of high prevalence.[43] IDH is a chronic, relapsing syndrome that usually affects young children.[44] T-cell infiltration is observed in skin lesions from patients with IDH,[45] and it is possible that both HTLV-I-infected cells and activated T-cells migrate to the skin of these patients.[46] It has recently been observed that 30% of patients with IDH develop juvenile HAM/TSP[47] and that this skin manifestation probably represents a risk factor for the development of ATLL.[20,48,49]

The major diagnostic criteria for IDH proposed by La Grenade *et al.*[50] in 1998 include the following: (i) dermatitis of the scalp, axillae and groin, external ear and retroauricular areas, eyelid margins, paranasal skin, and/or neck; (ii) chronic watery nasal discharge without other signs of rhinitis and/or crusting of the anterior nares; (iii) early childhood-onset or chronic relapsing dermatitis; and (iv) HTLV-I antibody seropositivity. Among the minor or less specific criteria are positive cultures for *Staphylococcus aureus* and/or *β-hemolytic streptococci* from the skin or the anterior nares, generalized fine papular eruption, generalized lymphadenopathy with dermatopathic lymphadenitis, anemia, elevated erythrocyte sedimentation rate, hyperimmunoglobulinemia, and elevated CD4 counts, CD8 counts, and CD4/CD8 ratio.

The diagnosis is based almost exclusively on the clinical aspects of the disease, and it is therefore necessary to differentiate it from atopic dermatitis and seborrheic dermatitis. Histopathological examination shows similar features to other types of chronic dermatitis.[51] Like

other forms of dermatitis, histologically, IDH may represent as a benign simulator of MF.[45] The disease responds to antimicrobials and corticosteroids (topical and/or systemic), but relapses occur when antimicrobials are withdrawn.

Sjögren's syndrome (SS)

The pathogenesis of SS has been discussed from the perspective of both clinical and molecular mechanisms. Among them, viral infection has been speculated to be a possible trigger of SS.[52] In clinical reports and murine experiments, HTLV-1 has been implicated as a causative agent in some patients with SS.[53,54] A higher prevalence of HTLV-1 antibodies in primary idiopathic polymyositis (PM) patients compared with that of the general population has been previously reported in studies from Jamaica, Martinique, and Japan.[55–57] The pathogenesis of the HTLV-1-positive PM is not clearly known and seems to be related to an immunological process and/or direct infection of the muscle fibers by the virus.[58,59]

Infectious complications

Crusted scabies

Crusted scabies is an infrequent but severe infection caused by massive infestation with *Sarcoptes scabiei var. hominis*. Crusted scabies has been reported in patients receiving immunosuppressive therapies, such as corticosteroids or radiotherapy, as well as in patients with HTLV-1 infection, leukemia, HIV infection, Down's syndrome, lepromatous leprosy, diabetes, Bloom's syndrome, and occasionally in apparently healthy patients.[60] In a Brazilian study including 91 cases of scabies, crusted or severe forms were strongly associated with HTLV-1 and, to a lesser degree, with HIV infection.[61]

Leprosy

A high prevalence of HTLV-1 in patients with leprosy has been reported in surveys from the Ivory Coast, Congo, and Kinshasa in Africa, and Kyushu in Japan. HTLV-1 infection, however, was rare in patients with leprosy in New York.[62] Nobre *et al.*[63] studied the seroprevalence of HTLV-1 infection in 1229 patients attending a dermatology outpatient clinic in Brazil. Two cases of leprosy were recorded among nine HTLV-1 carriers.

Strongyloidiasis

The risk of developing strongyloidiasis is twice as high among HTLV-1-infected people as among healthy controls.[64] The disseminated form of strongyloidiasis, also referred to as hyperinfection, has been described in patients with malignant tumors, severe malnutrition, corticosteroid or cytotoxic therapy, renal transplantation, and HTLV-1 infection.[64,65]

Conclusion

Thirty years after its first description, HTLV-1 is still a poorly recognized infection. Many carriers remain asymptomatic, which contributes to the silent transmission of the virus. Dermatological complications are present and should be recognized particularly when dealing with patients proceeding from an endemic area. The most important dermatological-related events in HTLV-1 are IDH in patients from other HTLV-1 endemic regions rather than Japan and ATLL, which should be differentiated from MF and other CTCL in patients from endemic areas. Prompt recognition of the infection may affect the prognosis and therapy.

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