Netherlands
The Journal of Medicine

CASE REPORT

Adult T-cell leukaemia and lymphoma: report of two cases and a brief review of the literature

H.C.T. van Zaanen*, J.G. Pegels

Department of Internal Medicine and Haematology, Sint Franciscus Gasthuis, Kleiweg 500, 3045 PM Rotterdam, the Netherlands, tel.: +31 (0)10-461 61 61, fax: +31 (0)10-461 26 92, e-mail: h_van_zaanen@franciscus.nl, * corresponding author

ABSTRACT

Human T-cell lymphotropic virus type 1 (HTLV-1) can cause adult T-cell leukaemia/lymphoma (ATLL). Two patients originating from the Caribbean area with ATLL are described. The first patient developed respiratory insufficiency due to acute T-cell leukaemia. The diagnosis was suspected because of characteristics of abnormal lymphocytes in the blood smear. The second patient had lymphadenopathy and developed severe hypercalcaemia. Both patients were typical cases of ATLL. The pathogenesis, clinical manifestations, pitfalls and treatment of this intriguing disease are discussed.

INTRODUCTION

Infection with human T-cell lymphotropic virus type 1 (HTLV-1) may cause a distinctive malignancy, adult T-cell leukaemia/lymphoma (ATLL). The clinical features of ATLL can be divided into four different subtypes; acute, chronic, smouldering, and a lymphoma type. This HTLV-1-associated malignancy occurs mainly in Japan, the Caribbean area, Africa and parts of South America. This disease is rare in Europe. We describe two patients originating from the Caribbean with ATLL, one suffering from an acute T-cell leukaemia and the other from the lymphoma type. We also discuss the possible pitfalls of this disease, such as hypercalcaemia and infection with *Strongyloides stercoralis*.

CASE REPORT

Patient 1

A 36-year-old female was admitted to the pulmonary department of our hospital because of rapidly progressive shortness of breath. She was born in French-Guyana and had never been ill before. On physical examination she was tachypnoeic with a breathing rate of 30/min. Physical examination of the chest revealed no abnormalities. The temperature was 38 °C, no lymph nodes were palpable, and liver and spleen were not enlarged. Laboratory examination showed lymphocytosis (leucocytes 34 x 10^9/L, with 32% atypical lymphocytes), elevated LDH 2684 U/L (normal value 450 U/L), and hypoxaemia; pH 7.42, pO_2 41.9 mmHg, pCO_2 32 mmHg, O_2 saturation 79%. Chest X-ray showed fine reticular infiltrates of both lungs. She was treated for atypical pneumonia with intravenous erythromycin, oxygen and inhalation treatment with salbutamol and ipratropium. HIV serology proved to be negative. Two days later she was transferred to the intensive care unit for mechanical ventilation because of respiratory insufficiency. A bronchoscope showed no abnormalities, but lavage showed atypical lymphocytes. The next day, the haematologist was asked to look at the blood smear, which showed typical cleaved and cerebriform lymphocytes (*figures 1* and *2*). The diagnosis of HTLV-1 infection with acute T-cell leukaemia was suspected and immediately confirmed by immunological typing of these lymphocytes; CD3/CD4 positive, CD8 negative, CD5 positive, CD25 positive and CD7 negative. Antibodies to HTLV-1 were positive. She was treated with CHOP chemotherapy (cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² and prednisolone 100 mg) and improved dramatically. After four days she could be transferred to the haematology department for further treatment.

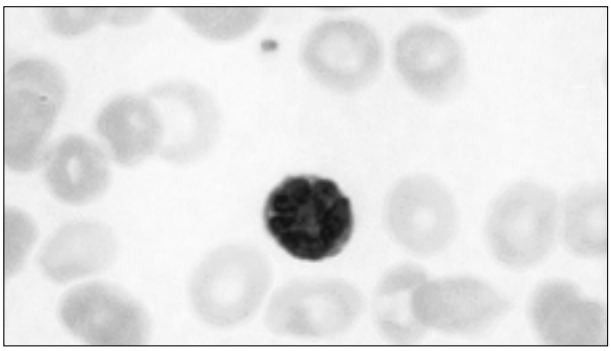

Figure 1
Cerebriform lymphocyte in the pheripheral blood of patient 1

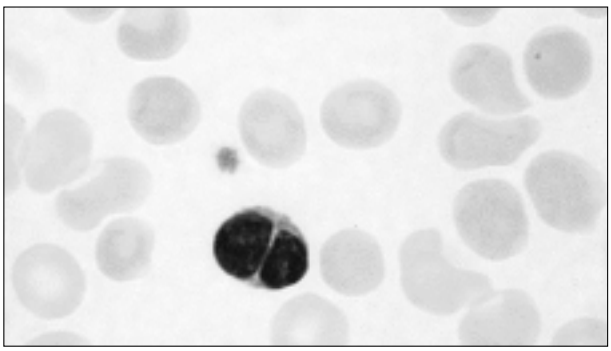

Figure 2
Cleaved lymphocyte in the peripheral blood of patient 1

Microbiological examination of the stool showed *Strongyloides stercoralis* for which she was successfully treated with ivermectine. She received cotrimoxazole (480 mg/day) as prophylaxis for *Pneumocystis carinii* pneumonia. The ATL was treated with six cycles of CHOP chemotherapy resulting in a clinical remission. Eleven months later the ATL relapsed, showing a rise in leucocyte count from 4.8 to 40.9 x 10^9/L with 88% lymphocytes, hypercalcaemia (calcium 2.91 mmol/L) and serum LDH elevated to 1454 U/L. No lymph nodes were palpable. The hypercalcaemia was treated with intravenous pamidronate. The ATL was treated with another two cycles of CHOP chemotherapy, followed by DHAP (dexamethasone, high ARA-C, cisplatinum), zidovudine/interferon-alpha, and fludarabine, respectively. Despite these efforts she died of refractory disease four months after the relapse. Her identical twin sister also appeared to be HTLV-1 positive, without any symptoms.

Patient 2

A 64-year-old man from Surinam was admitted to our outpatient clinic because of lymphadenopathy. Ten days previously he had noticed enlarged axillary and inguinal lymph nodes. He had no complaints of weight loss, night sweats or fever. On physical examination he appeared well, and had axillary and inguinal lymph nodes between 2 and 5 cm in diameter. Liver and spleen were not enlarged.

Laboratory examination showed no abnormalities, except for an elevated LDH of 589 U/L (normal value <450 U/L). Serum calcium was normal (2.42 mmol/L). Chest X-ray and sonography of the abdomen were normal. HIV serology was negative. Cytological punctures of different lymph nodes showed small lymphocytic cells between large atypical lymphoblasts with high mitotic activity. These cells were positive for CD3, CD4, HLA-DR and negative for CD7, CD8 and CD25. Bone marrow examination showed normal red, white, and megakarocyte distribution but with clusters of lymphocytes with identical immunological markers. A T-cell non-Hodgkin's lymphoma was suspected and HTLV-1 serology was performed, which proved to be positive. Before we could discuss these results with the patient, he was admitted to hospital because of severe somnolence. This was due to severe hypercalcaemia (serum calcium 4.52 mmol/L, albumin 32 g/L and LDH 1484 U/L). He was treated with intravenous pamidronate, resulting in an improvement in his clinical condition. It was concluded that this patient had an HTLV-1-associated T-cell NHL, stage 4A, and treatment with CHOP chemotherapy was started. Cotrimoxazole 480 mg daily was given for *Pneumocystis carinii* prophylaxis. *Strongyloides stercoralis* was not found in the stools of this patient. After six cycles of CHOP chemotherapy, physical examination and CT scan analysis showed a complete remission. Two months after the last cycle of chemotherapy, the disease relapsed with enlarged lymph nodes, elevated calcium level of 4.28 mmol/L and elevated LDH 680 U/L. Again he was treated with pamidronate and chemotherapy (dexamethasone, high-ARA and cisplatinum). Because of the minor response after two cycles of DHAP, zidovudine/interferon was given. Due to intolerance of this combination and because of severe pancytopenia, the latter treatment was stopped and fludarabine 25 mg/m^2 for five consecutive days was given. During this treatment he developed skin lesions with nodules and papules in the neck region and he became somnolent, which turned out to be due to involvement of the central nervous systems, which was apparent from the presence of malignant lymphocytes in the cerebrospinal fluid. Following the wish of the patient and his family, all treatment was stopped and he died soon afterwards.

DISCUSSION

Epidemiology and pathogenesis

Adult T-cell leukaemia/lymphoma (ATLL) was first reported in Japan in 1977.[1] ATLL is associated with the human T-lymphotropic virus type 1 (HTLV-1). HTLV-1 is an RNA-containing retrovirus, which is endemic in Japan, parts of South America, the Caribbean and areas of Central and West Africa. Our two patients originated from French-Guyana and Surinam, respectively.

In endemic areas of Japan, antibodies to HTLV-I are found in up to 37% of healthy adults.[2] However, only about 3% of carriers develop ATLL. ATLL only occurs in adults. The age of onset ranges from 24 to 85 years, with an average of 58 years. The aetiological association of HTLV-I and ATLL is based on a series of findings. First, areas of high incidence of ATLL correspond with those of high prevalence of HTLV-I infection. Second, all patients with ATLL have antibodies against HTLV-I. Third, HTLV-I proviral DNA can be found in ATLL neoplastic cells. Finally, HTLV-I immortalises human CD4 T cells.[3,4]

The incubation period of ATLL is long, ranging from 10 to 30 years, although ATLL acquired from blood transfusion may occur after a shorter period.[5]

HTLV-I is not easily transmissible, since cell-cell contact is generally required. Two major transmission routes have been described. One is vertical transmission from mother to child via HTLV-I positive lymphocytes in breast milk. The second important route is horizontal transmission through sexual contact, frequently from husband to wife, rarely from wife to husband. Virus-positive lymphocytes have been detected in semen of seropositive men. Two other transmission routes of HTLV-I are blood products containing infected T cells and intravenous drug abuse. In the Netherlands, every year 3 to 15 healthy blood donors are found to have antibodies against HTLV-I.[6]

Most of the effects of HTLV-I infection have been attributed to the HTLV-I-encoded protein Tax (trans-activator of X). This protein is a key regulator for immortalisation, transformation, and oncogenesis of the HTLV-I-infected lymphocytes through its interaction with many cellular proteins. Most of these proteins, including Tax, are not expressed at detectable levels in cells in ATLL. Their role in the leukemogenic process must therefore be limited to the early stages.[7,8]

Human T-lymphotropic virus type 2 (HTLV-II) was isolated in 1982 by Kalyanaraman from a patient with an unusual T-cell variant of hairy cell leukaemia. It has subsequently been isolated only rarely in lymphoid neoplasia, but is prevalent in intravenous drug abusers.[9]

CLINICAL MANIFESTATIONS

Four clinical subtypes of ATLL have been proposed.[10] First, the acute leukaemia type, representing 57% of the patients, in which a leukaemic manifestation of the disease is seen (patient 1). Hypercalcaemia and elevated LDH levels are common. Second, a lymphoma type (about 19% of the patients) without lymphocytosis and with histologically proven lymphadenopathy with or without extranodal lesions (patient 2). Third, a chronic type (about 19% of the patients) with more than 3.5 x 10^9/L T lymphocytosis, LDH value up to two times the normal upper limit, and no hypercalcaemia. Lymphadenopathy and involvement of liver, spleen and lung may be present. Finally, the smouldering type, representing the remaining patients, with a normal lymphocyte count, but with at least 5% abnormal T lymphocytes in peripheral blood, no hypercalcaemia, LDH value of up to 1.5 times the normal upper limit, and no lymphadenopathy or liver and spleen involvement.

The most common physical findings at presentation are lymphadenopathy, skin lesions, hepatomegaly and splenomegaly. Rapid development of diffuse peripheral lymphadenopathy without mediastinal involvement, as in our second patient, is typical. The skin lesions in ATLL are variable, including nodules and papules as in patient 2, localised erythema and plaques, and generalised erythroderma. A biopsy of skin lesions usually reveals dermal or epidermal infiltration of malignant T cells. The skin lesions in ATLL often resemble mycosis fungoides, a low-grade cutaneous T-cell lymphoma. Characteristically, mycosis fungoides progresses from an eczematous stage to plaques and finally to tumours. Circulating lymphocytes with cleaved or cerebriform nuclei are highly suggestive of ATLL (*figures 1* and *2*). This emphasises the importance of examination of the blood smear. The surface phenotype of ATLL cells characterised by monoclonal antibodies is CD3-positive, CD4-positive, CD7-negative, CD8-negative, and CD25-positive.[2] These findings suggest that ATLL cells originate from the CD4 subset of mature T cells.

Elevated serum calcium levels are seen in most patients with aggressive disease. Our two patients also developed this complication. Parathyroid-hormone-related protein (PTHrP), probably induced by Tax protein, is released from ATLL cells in patients with hypercalcaemia and stimulates osteoclasts.[11] There is a much lower rate of replication of HTLV-I than of HIV. HTLV-I can impair the immune response, but less dramatically than HIV. Opportunistic infections are frequent in patients with ATLL. The spectrum of agents that cause these infections is similar to that seen in AIDS, including protozoa, fungi and viruses. Strongyloidiasis (as in patient 1) is frequent and may be associated with hyperinfection and gram-negative bacteraemia, which is often fatal.[12] Other diseases associated with HTLV-I infection are HTLV-I uveitis and tropical spastic paraparesis with hyperreflexia, urinary bladder disturbances and muscle weakness.[2]

PROGNOSIS AND TREATMENT

Survival of patients with acute and lymphoma types of ATLL is poor, being 6.2 months for acute type, 10.2 months for lymphoma type and 24.3 months for chronic type ATLL. Several features were found to be predictive of shortened survival: poor performance status, age >40 years, hypercalcaemia, high lactate dehydrogenase, and increased

tumour bulk.[10] There is no consensus on the best available therapy for ATLL. For acute and lymphoma type ATLL, combination chemotherapy can be effective. Complete response rates of 30 to 40% are reported with different combinations of drugs (CHOP, MACOP-B, PROMACE), but no one regimen appears superior.[10,12] Although these combinations of chemotherapy have improved response rates, this has not translated into increased survival due to early relapse. Autologous and allogeneic bone marrow transplantation have been reported with little success.[13,14] The combination of zidovudine and interferon-alpha has activity against ATLL, even in patients in whom prior cytotoxic therapy has failed. With oral zidovudine (200 mg five times daily) and interferon-alpha (five to ten million units daily) subcutaneously, responses were achieved in 50 to 60% of the patients.[15,16] Profound pancytopenia is the major toxicity of this combination treatment in these high doses. We encountered such side effects in patient 2.

Central nervous system involvement may develop in as many as 10% of patients with ATLL.[17] Meningeal relapse after initial treatment may occur in patients not receiving prophylactic intrathecal therapy. Therefore, it is recommended that the cerebrospinal fluid is analysed at diagnosis and CNS prophylaxis is given to all patients with acute and lymphoma-type ATLL. Our two patients did not receive CNS prophylaxis, and in patient 2 meningeal involvement occurred at the end of the disease.

Prevention of infection is extremely important during treatment of ATLL. Prophylactic use of cotrimoxazole is now routine, but antifungal and antiviral agents should be considered in all patients with acute or lymphoma-type ATLL. Stools from all patients should be screened at diagnosis and any patients positive for *Strongyloides* should be treated appropriately.[10] In the first patient *Strongyloides* was found and was successfully treated with ivermectine.

Treatment of patients with ATLL remains disappointing. The best treatment is prevention of infection with HTLV-1. The most important way to achieve this is to discourage breastfeeding by women positive for HTLV-1 antibodies. We assume that the first patient and her identical twin sister were infected by breast milk. Because only a minority (<5%) of the HTLV-1 carriers develop ATLL, prophylactic antiretroviral treatment is not recommended at this moment. In most Western countries all donated blood is tested for HTLV-1 antibodies. No transfusion recipients have seroconverted since screening started, even among patients who have received many transfusions.

In summary, the blood smear remains a simple and effective examination, but is often undervalued. Severe hypercalcaemia can be one of the major symptoms of ATLL, especially in the acute and the lymphoma type. Stools of all patients with ATLL should be examined for *Strongyloides*. Finally, analysis of the cerebrospinal fluid in all patients with acute and lymphoma type ATLL is recommended at diagnosis, and these patients should be given CNS prophylaxis.

ACKNOWLEDGEMENT

The authors wish to thank Mr. W. de Vries of the Special Haematology laboratory for providing the figures.

REFERENCES

1. Uchiyama T, Yodio J, Sagawa K, et al. Adult T-cell leukemia: clinical and hematologic features of 16 cases. Blood 1977;50:481-92.
2. Yamaguchi K. Human T-lymphotropic virus type 1 in Japan. Lancet 1994;343:213-6.
3. Hattori T, Uchiyama T, Toibana T, et al. Surface phenotype of Japanese ATL cells characterized by monoclonal antibodies. Blood 1981;58:645-7.
4. Yamaguchi K, Seiki M, Yoshida M, et al. The detection of human T-cell leukemia virus proviral DNA and its application for classification and diagnosis of T-cell malignancy. Blood 1984;63:1235-40.
5. Chen YC, Wang CH, Su IJ, et al. Infection of HTLV type 1 and development of human T-cell leukemia/lymphoma in patients with hematologic neoplasms: a possible linkage to blood transfusion. Blood 1989;74:388-94.
6. Zaaijer HL, Lelie PN, Poel CL van der. Infectie met humaan T-lymfotroop virus bij Nederlandse bloeddonoren, 1993-1996. Ned Tijdschr Geneeskd 1997;141:1571-2.
7. Furukawa Y, Kubota R, Tara M, et al. Existence of escape mutant in HTLV-1 tax during the development of adult T-cell leukemia. Blood 2001;97:987-93.
8. Gallo RC. A surprising advance in the treatment of viral leukemia. N Engl J Med 1995;332:1783-4.
9. Thomson BJ, Dalgleish AG. Human retroviruses. Blood Rev 1988;2:211-21.
10. Shimoyama M. The Lymphoma Study Group (1984-87). Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma. Br J Haematol 1991;79:428-37.
11. Watanabe T, Yamaguchi K, Takatsuki K, et al. Constitutive expression of parathyroid hormone-related protein (PTHrP) gene in HTLV-1 carriers and adult T cell leukemia patients which can be transactivated by HTLV-1 tax gene. J Exp Med 1990;172:759-65.
12. Mufti GJ. Management of adult T-cell leukemia/lymphoma. Br J Haematol 1998;100:453-8.
13. Tsukasaki K, Maeda T, Arimura K, et al. Poor outcome of autologous stem cell transplantation for adult T cell leukemia/lymphoma: a case report and review of the literature. Bone Marrow Transplant 1999;23:87-9.
14. Borg A, Liu Yin JA, Johnson PRE, et al. Successful treatment of HTLV-1 associated acute T-cell leukemia/lymphoma by allogeneic bone marrow transplantation. Br J Haematol 1996;94:713-5.
15. Gill PS, Harrigton W, Kaplan MH, et al. Treatment of adult T-cell leukemia-lymphoma with a combination of interferon alfa and zidovudine. N Engl J Med 1995;332:1744-8.
16. Hermine O, Bouscary D, Gessain A, et al. Treatment of adult T-cell leukemia-lymphoma with zidovudine and interferon alfa. N Engl J Med 1995;332:1749-51.
17. Teshima T, Akashi K, Shibuya T, et al. Central nervous system involvement in adult T-cell leukemia/lymphoma. Cancer 1990;65:327-32.