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Research Article

Human T-Cell Lymphotropic Virus-1 Causing Diseases and Cancer in Human

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Abstract:

Human T-cell leukaemia virus-1(HTLV-1) is a kind of retrovirus which after entering in the human body reversely transcribed into several proviruses integrating the host genome develops a lethal blood cancer known as adult T-cell leukaemia (ATL). HTLV-1 also develops some other life threatening diseases like HTLV-1 associated myelopathy or tropical spastic myelopathy (HAM/TSP) in human. The present paper is an attempt to discuss discovery, epidemiology, diagnosis and transmission of the virus with their diseases and cancer causing abilities in the light of recent researches done so far in the field of microbial origin of cancer.

Keywords: HTLV-1, Retrovirus, Diseases, Cancer, ATL, HAM, TSP.

Introduction

Human T-cell lymphoma virus (HTLV-1) is a kind of retrovirus infecting the T-cell of white blood corpuscles developed adult T-cell leukaemia (ATL) in humans. This is lymphocytic blood cancer occurring usually at the age of 62. ATL is an aggressive non-Hodgkin lymphoma and multiple myeloma developing osteolysis and hypercalcaemia usually accompanied by the visceral involvement, skin and bone lesions causing breast, prostate and lung cancer. The virus in addition to ATL also develops progressive neural disorder as HTLV-1 associated myelopathy or tropical spastic paraparesis (HAM/TSP) (Ishitasuka and Tamura 2014, Mc Kendall 2014, Charles and Ratner 2015, Oliveira *et al.* 2018) [1-4]. But, despite all these investigations this is still not very clear that why some people infected with the virus developed the disease while others remain asymptomatic throughout their lives? The present paper deals with the study of human T-cell leukaemia virus for their life-threatening disease-causing abilities and the development of lethal cancers in human. This is an outcome of recent researches carried out in the same field.

Discovery of the virus

The disease was discovered in 1977 in Japan and the virus was isolated in 1980 from a patient originally thought to have been suffering from cutaneous lymphoma. Surprisingly, after an examination not only the virus but the lymphoma caused by them were also found different causing acute T-cell leukaemia/Lymphoma (ALT). Later on, a chronic disease of the spinal cord was also investigated with the infection of the same virus as HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). The same discovery was again verified by the investigations made by the Francis Ruscetti and his coworkens (Poiesz *et al.* 1981, Verdonck *et al.* 2007)[5,6].

Epidemiology of the virus

Approximately 10 million people around the world are infected by the HTLV-1. Quite surprising the women are being infected double in number than men.This is prevalently found in southern Japan, Taiwan, Fujian, Iran , Papua New Guinea, Caribbean, Equatorial Africa, Middle East, South America, Melanesia and in some parts of the Australia. The highest prevalence of HTLV-1 infection is 1% in Japan. (Verdonck *et al*. 2007, Gonclaves 2010, Chihara *et al*. 2012, Satake *et al*.2012, Nosaka *et al*. 2017, Anat *et al*. 2018) [6-11]

Diagnosis of the disease

Circulating leukocytes in blood and atypical lymphocytes as flower cells in blood smears are frequently seen in an infected person. Similarly, the virus has been detected in cervical secretions and serum, their antibodies are also detected in serum and the cerebrospinal fluid. However, despite current routine practices other confirmatory screening tests must be followed as immunoassays, western blot and radio immuno-precipitation assay (RIA) to confirm the infection and disease (Verdonck *et al*. 2007) [6].

Clinical symptoms of the disease and cancer

Adult T-cell leukaemia/lymphoma is characterized by blood,

bone marrow and brain involvement hypercalcaemia and lytic bone lesions (Charles and Ratner 2015)][3].HTLV-1 has also been found in producing cutaneous T-cell lymphoma , HTLV-1 associated myelopathy (HAM) or tropical spastic paraparesis (TSP). This progressive demyelinating upper motor neuron disease is characterized by the sensory and motor deficits of the lower extremities, incontinence and the impotence with erectile dysfunction in men and several sexual disorders in human female (Verdonck *et al*. 2007, Mc Kendall 2014, Araujo 2015, Oliveira *et al*. 2017, Lopes *et al*. 2018) [2,6,12-14].

Further, some other symptoms are clonus, bladder dysfunction with cancer, rheumatoid arthritis, intermediate uveitis and getting a risk of several opportunistic infections. These opportunistic infections are developed due to the weakened immune system. It produces sepsis, chronic lung disease with pneumocystis pneumonia, infections like *Staphylococcus aureus*, hyperinfections like *Strongyloides stercoralis* leading to death. Other opportunistic infections of HTLV-1 patients are dermatitis, histoplasmosis, scabies and eczema (Gotuzzo *et al*. 2007, Ishitasuka and Tamura 2014, Silva *et al*. 2013, Mc Kendall 2014, Nosaka *et al*. 2017, Oliveira *et al*.2018) [1,2,4,10,15,16].

Transmission of the virus

Human T-cell leukaemia virus is spread either sexually or by sharing needles, blood transfusions, vertical transmissions and breast feeding. While only 5% children are infected vertically, more than 25% infants are infected by breast feeding from infected mothers. In fact, the HTLV-1 is more easily transmitted through indirect contact with the help of bodily fluids like breast milk, genital secretions and semen. Further, as mother- to- child transmission (MTCT) has always been one of the most important modes of transmission of the virus very little is done in the world to avoid HTLV-1 transmission from mother to child. Japan and UK are the only countries included the HTLV-1 antenatal screening in their national programmes (Bigger *et al*. 2006, Amor *et al*. 2013, Perches *et al*. 2016)[17-19].

Oncogenicity of the virus

Most people with HTLV-1 are asymptomatic however, several diseases developed have been associated with the virus. The development of adult T-cell leukaemia or lymphoma is one of them. This is in general characterized by the lymphadenopathy, hepatosplenomegaly, hypercalcaemia via the involvement of skin, lung , bones and other organs. ATL is a rare blood cancer of immune T-cells caused by the HTLV-1. The virus has got a long latency period to cause ATL. There are four types of ATL found in nature. These are acute smoldering, lymphoma type and chronic. ATL is more prevalently occurring at the age of 62. (Nicot 2005, Chihara *et al*. 2012, Charles and Ratner2015, Oliveira *et al*. 2018) [3,4,8,20].

HTLV-1 virus develops leukaemia or lymphoma in human. However the incubation period differs for the development of cancer geographically. It appears that this is 60 years for Japanese and 40 years in the Caribbean. Chronic inflammation at the cytokine level in the lymphocytes produces lymphoma in humans. HTLV-1 reversely transcribed DNA integrating into the cellular DNA behaving as a provirus spread through viral synapse. An affected person carries tens of thousands of clones of HTLV-1 lymphocytes, each with their own cloned integration site of the provirus in the host genome (Matsuoka and Jeang 2007, Charles and Ratner 2015) [3,21].

Further, the HTLV-1 infects the $CD4^{+}$T lymphocytes to modify their functions in such a way that autoimmunity developed triggering the uncontrolled inflammatory reactions that can lower the immunity of the host. It changes the lymphocytic DNA resulting into the disruption of gene function developing leukaemia (Anat *et al*.2018). These effects are mediated by the production of reactive oxygen species, DNA damage and the disturbances in the repair process with the inactivation of p53 and resistance to apoptosis (Charles and Ratner 2015) [3].

Treatment of the Disease

There is no cure for the treatment of asymptomatic carrier. However , considering a lifelong condition only symptomatic relieves are being provided to the patients of ATL, HAM/TSP with the use of chemotherapy, antiretroviral and immunotherapies. The most preferred treatments of ATL is α- interferon, α-interferon with zidoviudine, R-CHOP with arsenic trioxide, corticosteroids, plasmapheresis and the use of valproic acid (Gonclaves *et al.2010)* [7] . Recently, Pralatrexate and mogamutizumab have also been applied for the same treatment (Marneros *et al . 2009*, Subramaniam *et al . 2012)* [22,23].

The prognosis of the disease is very slow . There is a long latent period between the infection of HTLV-1 and the ATL development . This is usually longer than 20 years. However, most of the patients die within a year of fully blown disease development .A coordinated team of specialists can only manage the situation safely if the disease is developed in a patient. It has been observed that the patients are unable to walk unassisted within 10 years and always require a wheelchair within 20 years after onset of the disease.

This is a disabling neurodegenerative disease that greatly affects the quality of life of a patient. Symptomatic relieves are to be given to the patients as and when required. Antiinflammatory , antidepressants and antiepileptic drugs are prescribed for pain and other sensory symptoms as paresthesias. Spasticity or stiffness is treated with the help of certain relaxants such as diazepam and beclofen. Sometimes, physical therapies also work well. Botulinic toxin may also be given. Anticholinergic drugs are given for the relief of urinary problems. Stool softeners and laxatives are also prescribed (Matsuoka and Jeang *2007*) [21].

Conclusion

HTLV-1 is a retrovirus develops in addition to adult T-cell leukaemia (ATL), the other related disease also known as

HTLV-1 associated myelopathy (HAM)/tropical spastic paraparesis (TSP). Approximately, 2 to 5 % of people with HTLV-1 will develop ATL, a cancer of the T-cell of white blood corpuscles. This is characterized by the fatigue and fever, constipation, nausea and vomiting, thirst, lymphadenopathy, pneumonitis, uveitis, Sikka syndrome as the dryness of mouth and eyes, Sjogren's syndrome, arthritis, thyroid problems, enlarged liver and spleen, skin and bone abnormalities, hypercalcaemia and lytic bone lesions, urinary urgency and numbness or pain in the lower limbs.

Similarly, the same virus develops HAM/TSP a progressive neuron disease may include the symptoms as neuropathy, myopathy, amyotrophic lateral sclerosis like syndrome, cognitive disorder, tremor and cerebrospinal syndrome. The same individuals may also show the symptoms as progressive stiffness and weakness of the lower limbs, lower back pain, fibromyalgia, ulcerative colitis and bowel and bladder dysfunction. Further, the disease also develops the enhanced susceptibility to opportunistic infections as *Staphylococcus aureus*, dermatitis, histoplasmosis, scabies, eczema and hyper infections like *Strongyloides stercoralis* leading to death.

Adult T-cell leukaemia is a kind of blood cancer of immune T-cells of lymphocytes developed by the HTLV-1 virus. Chronic inflammations caused by the virus produces lymphoma in humans. ATL is usually developed in humans at the age of 62 There are four types of ATL found in humans. They are acute, smoldering, lymphoma type and chronic. The HTLV-1 retrovirus reversely transcribed DNA in the form of proviruses integrated into the host genome triggering the uncontrolled inflammations and divisions of $CD4^+$T, lymphocytes producing a blood cancer as leukaemia in the host.

Finally, there are some ill understood facts regarding the HTLV-1 virus developing diseases in humans. Some of them are as under:

1. Why most of the people are asymptomatic throughout their lives while others develop the disease very easily.
2. There are very limited data available about the impact of HTLV-1 infection on fertility in humans. However, there are some reports available about the erectile dysfunction in men and sexual disorders in humans female.
3. Very little is known about the oral transmission and digestive tract infections of HTLV-1 virus in humans.
4. Lastly, as mother-to-child transmission (MTCT) of human T-cell lymphotropic virus-1 causes lifelong infection in children, further studies are required to better understand the prophylactic measures of the same problem. Similarly, very little is known about the intra-uterine infection of the same virus. More researches are still required to explore the truth.

Abbreviations

HTLV-1	Human T-cell leukaemia virus-1
ATL	Adult T-cell leukaemia
HAM	HTLV-1 associated myelopathy
TSP	Tropical spastic paraparesis
WBC	White blood corpuscles
RIA	Radio immuno precipitation
MTCT	Mother to child transmission
DNA	Deoxyribonucleic acid
p53	Tumor suppressor gene
$CD4^+$	Cluster of differentiation 4
R-CHOP	Rituximab-cyclophosphamide-hyroxydaunorubicin-oncovin-prednisone regimen

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Ethical clearance

Since the article is purely a review work hence it does not require an ethical clearance.

Conflict of interest

The authors have declared that no competing interests exist amongst us. They have approved the final version of the manuscript contributing equally.

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