

The role of human T-lymphotropic virus (HTLV) in cardiovascular diseases: A review of literature

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Review Article

Abstract

Cardiovascular diseases are a major cause of morbidity and mortality. Chronic inflammation is an important risk factor for atherosclerosis, and viral infections can cause cardiovascular disease by developing inflammation. Infection with human T-lymphotropic virus (HTLV) is endemic in some parts of the world such as Japan, Africa, Caribbean islands, South America, and Iran. HTLV-1 is an oncogenic retrovirus, and can cause adult T-cell leukemia/lymphoma (ATL or ATLL). It also causes HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP). A number of inflammatory diseases such as uveitis, arthritis, and Sjogren's syndrome are also associated with the virus. A few case reports have shown the direct involvement of the heart in HTLV-1-positive patients who develop ATLL. The purpose of this study was to review the literature relevant with the role of HTLV in cardiovascular diseases.

Keywords: Cardiovascular Disease, HTLV Infection, Atherosclerosis

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Introduction

Atherosclerosis which is the main cause of cardiovascular diseases, is a condition of chronic inflammation.¹ Infection with viral and bacterial agents are today recognized as a possible risk factor for atherosclerosis alongside other risk factors such as hypertension, smoking, hypercholesterolemia, hyperglycemia, and genetic factors.^{1,2} Examples of viral pathogens found in atherosclerotic plaque are: cytomegalovirus (CMV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), herpes simplex viruses (HSV), and Epstein-Barr virus (EBV).^{2,3} Therefore, other viruses could be potential risk factors for cardiovascular diseases, too.

Human T-lymphotropic virus type 1 (HTLV-1) is a member of Deltaretrovirus genus of the subfamily Orthoretrovirinae, Retroviridae family which mainly infects T-lymphocytes.⁴

HTLV-1 is an oncogenic retrovirus, and can cause adult T-cell leukemia/lymphoma (ATL or ATLL).⁵ It is also the causative agent for a neurologic disease named HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP).⁶ Fortunately, these conditions occur

in a small percent of the infected individuals, and more than 95% of them remain as asymptomatic carriers throughout their lives.⁵

We intend to review the available literature concerning the cardiovascular effects of HTLV infection. To obtain a comprehensive overview of the available information, we searched the PubMed and Scopus databases with the terms "HTLV", "ATLL", "cardiovascular", "cardiac", and "heart".

Virus structure

The structure of HTLV-1 is similar to other retroviruses. Its capsid contains two simple RNA strands together with the reverse transcriptase and integrase enzymes.⁷ Its genome contains structural and enzymatic genes: gag, pro/pol, and env, which are flanked by two long terminal repeats (LTRs). The pX region which is located between the env gene and the 3'-LTR codes for the Tax (p40), Rex (p27), p12, p13, p21, and p30 regulatory proteins. Among these, Tax has an especially important role in viral persistence and pathogenesis.⁸ Another important gene is HTLV-1 b-ZIP factor (HBZ)

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which is encoded from the 3'-LTR in the complementary strand of the genome. HBZ functions in two different forms, its mRNA form promotes cell proliferation, and its protein form downregulates Tax expression.⁷

P12 functions to promote viral escape from the immune system by different mechanisms, one of which is interaction with the interleukin-2 (IL-2) receptor.⁸ The p30 protein acts as a negative post transcriptional regulator through the nuclear retention of Tax/Rex RNA, and promotes viral latency.⁹ As with all retroviruses, HTLV-1 infects cells permanently.⁸

Epidemiology

HTLV infection is reported from all over the world. Certain parts of the world in which the prevalence rate of HTLV infection is more than 1% are assumed as endemic areas,¹⁰ such as Japan, Africa, Caribbean islands, South America,¹¹ and northeastern of Iran.^{12,13} The prevalence ranges between 1% to 10% in the general population of the mentioned areas; southern Japan have the highest prevalence.¹³⁻¹⁵ It is estimated that 10 to 20 million individuals are infected with the virus throughout the world.¹⁵

There are three main cities in northeastern of Iran in which HTLV infection is prevalent, Mashhad,¹⁶ Neyshabour,¹³ and Sabzevar¹⁷ with the prevalence rate of 2.12%, 7.2%, and 1.66%, respectively.

The transmission of this virus occurs through infected cells. Cell-free virions are said to be poorly infectious. Therefore, the virus is transmitted via four main routes: mother to child transmission which is mainly through breastfeeding, sexual transmission with a higher transmission rate from men to women, through contaminated blood products, and transmission between intravenous drug users.^{14,15}

HTLV-1-associated diseases

ATL and HAM/TSP are the two important diseases caused by HTLV which develop only in a small percentage of patients infected with the virus.

ATL is the malignancy of cluster of differentiation 4 (CD4⁺) T-lymphocytes and as mentioned earlier, the Tax protein is responsible for the abnormal growth of cells infected with HTLV-1. This poor prognosis malignancy usually presents with lymphadenopathy, hepatosplenomegaly, and skin lesions.¹⁵

HAM/TSP is a debilitating neurodegenerative disease on which current treatments have had poor effect.¹⁸ Studies on the pathogenesis of central

nervous system (CNS) involvement by HTLV-I have shown that the indirect involvement of the nervous system by lymphocytes is more probable than the direct attack of the virus to the neurons.⁶ Paraparesis of the lower limbs, which appears gradually, is the most common clinical feature.¹⁵

Other inflammatory diseases

HTLV-1 may cause many other inflammation-based diseases including uveitis and keratoconjunctivitis sicca in the eye,¹⁹ Sjogren's syndrome,²⁰ arthritis,²¹ polymyositis,²² and systemic lupus erythematosus (SLE).²³

Autoimmunity

HTLV-1-infection induces both the cellular and humoral immune responses. The immune dysregulation caused by the virus may play an important role in the development and pathogenesis of the associated diseases.²⁴

Changes in the systemic immune response has been seen in HTLV-1-infected patients, even in those who are asymptomatic. The virus induces changes in the activity of regulatory CD4 T-cell molecules which affect the homeostasis of cytokines, including interferon gamma (IFN- γ), tumor necrosis factor alpha (TNF- α), transforming growth factor beta (TGF- β), and IL-10. This disrupts the balance between inflammatory and anti-inflammatory responses, and leads to the loss of tolerance and the development of autoimmunity.⁷

Co-infection with other viruses

It has been shown that HTLV-1/HCV co-infection can increase liver disease and liver cancer mortality, and thus leads to the hypothesis that an immune modulation and inflammatory cytokine dysregulation is caused by HTLV-1, and causes progression to liver disease.^{25,26} It has also been discussed that T-cells infected with HTLV-1 can trigger a virus-specific immune response, and can increase cytokine production.²⁴

Chronic inflammation

Two mechanisms are proposed for the role of inflammation caused by microorganisms in atherosclerosis, the direct mechanism which is related to the infection in the vessel wall, and the indirect mechanism which is related to the increased secretion of cytokines.²⁷ HTLV-1, like many other viruses, activates the immune system's response.

Eradication of the pathogen is the main goal of this response, and it is done through an inflammation mechanism which involves the release of several cytokines and chemokines.²⁸

A number of studies have revealed evidence related to the presence of chronic inflammation in HTLV-1 affected individuals. For example, it has been shown that patients infected with HTLV-1 have a greater carotid intima-media thickness (IMT) than healthy subjects.²⁹

In a retrospective study in Iran, the seroprevalence of HTLV-1 was assessed in patients with cardiac symptoms, and was compared with the general population. It showed that patients with cardiac symptoms were nearly 3 times more infected with HTLV-1.³⁰

It is confirmed that HTLV-1 infects regulatory CD4⁺FOXP3⁺ T-cells which facilitates persistent infection. This pattern could contribute to the pathogenesis of the virus-associated diseases.²⁸

The concurrency of HTLV-1 and the inflammatory diseases mentioned earlier supports the inflammatory role of the virus in causing cardiovascular disease.¹⁹⁻²³

HTLV-1 and cardiovascular diseases

In general, cardiovascular diseases refer to the diseases of the heart, vascular diseases of the brain, and diseases of blood vessels. Among these, a subgroup of the diseases of the heart -called ischemic heart diseases which include angina and myocardial infarctions- and also the cerebrovascular disease and hypertension are related to atherosclerosis, and impose a great burden on health services.³¹

It has been demonstrated that the presence of antibodies against specific infectious agents increases the risk of cardiovascular disease. Among them, many viruses have been studied widely but due to the epidemiology of HTLV-1 and its regional distribution, its relation with atherosclerosis and cardiovascular disease has only been explained in few studies.³⁰

Regarding the relationship between HTLV-1 and non-atherosclerotic heart diseases such as heart failure, myocarditis, and cardiomyopathies, the scientific literature is limited to a few case reports which are discussed later in this article.

As the main cause of myocarditis is viral infections, it would be wise to consider HTLV-1 as a possible etiology for the disease, and test patients

suffering from myocarditis for this virus infection.

Cardiovascular autonomic dysfunction

Ohishi et al. showed that the mean systolic and diastolic blood pressures were lower in patients with HTLV-associated myelopathy (HAM) than in healthy subjects; while the mean heart rate was higher in patients than controls. They thus suggested that subclinical cardiovascular autonomic dysfunction can be found in patients with HAM.³²

Case reports

A number of cases are reported regarding the involvement of the heart in patients diagnosed with ATLL due to HTLV-1 infection.

In 1993, Gabarre et al. found T-cell non-Hodgkin's lymphoma in the aortic and mitral valves in a 60-year-old Iranian woman whose serum was positive for HTLV-1 antibodies.³³

Daisley and Charles described a case of metastatic calcification of the heart, lungs, and kidneys in a man who had an HTLV-1-associated lymphoma.³⁴

In 1997, the same authors reported three autopsy cases of HTLV-infected subjects who had lymphoma/leukemia affecting the heart; although none of the three patients had ante-mortem manifestation of cardiac involvement. Their cardiac involvement varied from microscopic foci to macroscopic infiltration mimicking myocardial infarction.³⁵

Furukawa et al. reported metastatic calcification in the myocardium of a 52-year-old man with ATLL which caused heart failure and death; but the ATLL cells did not infiltrate in the myocardium.³⁶

Toyama et al. reported a case of lymphoma-type ATL with initial massive cardiac involvement presenting as tumors in the right atrium.³⁷

Shepherd et al. discussed a case of fatal cardiovascular instability due to hypercalcemia in a patient with ATLL. Their patient who was diagnosed with HTLV-1 infection and ATLL only after death, had extensive intra- and extracellular calcium deposition in her myocardium and other organs due to ATLL.³⁸

A summary of the related studies is shown in table 1.

Conclusion

The literature relevant with the cardiovascular effects of HTLV-1 are scant, and are limited to a number of case reports and a few retrospective studies.

Table 1. The summary of the studies regarding the effect of human T-lymphotropic virus type 1 (HTLV-1) infection on the heart

Study type	Year	Author	Key finding
Case control	2014	Layegh et al. ²⁹	Greater carotid intima-media thickness in patients infected with HTLV-1
Case control	2013	Farid et al. ³⁰	Patients with cardiac symptoms are 3 times more infected with HTLV-1 than healthy controls
Case control	1993	Ohishi et al. ³²	Cardiovascular autonomic dysfunction in patients with HTLV associated myelopathy
Case report	1993	Gabarre et al. ³³	T-cell lymphoma in cardiac valves
Case report	1993	Daisley and Charles ³⁴	Calcification in the heart in a patient with lymphoma
Case report	1997	Daisley and Charles ³⁵	3 cases of lymphoma affecting the heart
Case report	1991	Furukawa et al. ³⁶	Calcification in the myocardium in a patient with lymphoma
Case report	2002	Toyama et al. ³⁷	Cardiac involvement in a patient with lymphoma
Case report	2016	Shepherd et al. ³⁸	Calcium deposition in the myocardium in a patient with lymphoma

HTLV-1: Human T-lymphotropic virus type 1

Aside from the direct involvement of the heart itself in HTLV-1-positive patients who develop ATLL, evidences indicate that HTLV-1 could cause atherosclerosis and cardiovascular disease.

It is therefore necessary to examine HTLV-1-infected patients' cardiovascular system on a routine basis, even in asymptomatic carriers.

The calcification seen in the myocardium of a number of patients affected with HTLV-1 makes necessary the study of this biochemical change, and its relying cause in those patients.

More practical studies are to be done to confirm the concept of the role of HTLV-1 in atherosclerosis which lead to cardiovascular disease.

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Conflict of Interests

Authors have no conflict of interests.

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