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Chagas' disease and AIDS

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Abstract

Chagas' disease caused by *Trypanosoma cruzi* is an opportunistic infection in the setting of HIV/AIDS. Some individuals with HIV and chronic *T. cruzi* infection may experience a reactivation, which is most commonly manifested by meningoencephalitis. A reactivation myocarditis is the second most common manifestation. These presentations may be difficult to distinguish from toxoplasmosis in individuals with HIV/AIDS. The overlap of HIV and *Trypanosoma cruzi* infection occurs not only in endemic areas but also in non-endemic areas of North America and Europe where the diagnosis may be even more difficult. The pathological features, diagnosis and the role of cytokines in the pathogenesis of the disease are discussed.

Background

In recent years there has been an increasing appreciation that Chagas' disease, caused by *Trypanosoma cruzi*, can be an opportunistic infection in the setting of HIV/AIDS. Before co-infection with HIV and *T. cruzi* was recognized as a syndrome, it was well known that patients with chronic Chagas' disease who became immunosuppressed could have a reactivation of their infection.

In the two decades since human immunodeficiency virus (HIV) infection was first described in the United States, diverse viral, bacterial, and fungal pathogens have been identified as causative agents of opportunistic disease. As our understanding of the pathogenesis and the natural history of these agents has grown, it has become clear that these infections are the inevitable consequence of T-cell depletion and depressed cell-mediated immunity. While *Pneumocystis* pneumonia and *Toxoplasma* encephalitis are common in the setting of advanced acquired immunodeficiency syndrome (AIDS), Chagas' disease in the setting of HIV infection is less commonly reported. However the reports of Chagas' disease in AIDS and after blood transfusions and organ transplants highlight the potential for the reactivation of parasitic diseases with advanced immunosuppression accompanying HIV infection.

The high prevalence of both HIV infection and parasitic diseases in the tropical and sub-tropical world has allowed for frequent overlap. Given the immunologic impact of HIV infection, it is understandable that concurrent infection would adversely affect the progression and natural history of parasitic infections. Considerable evidence has accumulated demonstrating the bi-directional interactions between parasitic diseases and HIV/AIDS and the deleterious influence on the natural histories of both [1-5].

Parasitic diseases have been shown to cause enhanced and prolonged immune activation [2,6]. Chronic immune activation by parasites is associated with several significant immunologic features. A decline in CD4+ and CD8+ cells, impaired natural killer activity, increased T-cell

apoptosis, and cellular anergy have all been demonstrated. These changes have been linked to the preferential activation of the Th2 type response, which in turn downregulate the Th1 type response, hinder macrophage activity, and weaken the cytotoxic T-cell response [1,6]. Such responses may lead to a deleterious interaction with HIV infection.

Some parasitic infections elicit the early production of IL-4, which eventually promote a Th2 type response. Given that Th1 mediated cytokines appear crucial in the containment of HIV infection, the immunologic changes associated with a predominantly Th2 type response have been implicated in the progression of HIV infection in the setting of various parasitic diseases [1,6,7]. Parasitic infection is linked to immune activation, which appears to play an important role in the progression of HIV disease. In turn, the progression of HIV disease may be associated with the immunosuppression that promotes the reactivation, parasitemia, and clinical manifestations of parasitic disease [3,6-8]. For example, recent studies in Uganda have demonstrated that clinical malaria and parasitemia are significantly more common in HIV-seropositive persons. Studies of pregnant women in Malawi have shown an increased incidence of malaria in those infected with HIV [9]. Moreover, clinical data demonstrate a higher HIV RNA count in persons infected with malaria and a subsequent reduction in the viral load after malaria treatment. Although this does not necessarily prove a cause and effect linkage, studies in mice have shown a significant increase in viral p24 after infection with *Plasmodium* [2,10]. Another parasitic infection of the tropics, leishmaniasis is appreciated as an opportunistic infection in individuals with HIV infection. *In vitro* studies have shown increased intracellular growth of *Leishmania* in HIV-infected macrophages. More than half of co-infected persons have detectable parasitemia reflecting uncontrolled multiplication and dissemination [2]. Although African trypanosomiasis and HIV infection co-exist in sub-Saharan Africa there are no solid epidemiologic data suggesting that the clinical course of one is exacerbated by the other.

Clinical disease and epidemiology of Chagas' disease

Chagas' disease or American trypanosomiasis, has a widespread distribution from Mexico to Argentina. Although autochthonous cases in the United States are extremely rare, the confluence of factors including immigration and AIDS have led to its emergence as a potential opportunistic infection in immunocompromised persons in Central and South America. *T. cruzi* has a complex life cycle that occurs in insect vectors and mammalian hosts. The vector, triatomine insects, become infected when it takes a blood meal from a mammal with circulating trypomastigotes. These forms transform into epimastigotes in the insect gut and multiply extracellularly. The epimastigotes ultimately migrate to the hindgut where they differentiate into non-dividing metacyclic trypomastigotes, which are discharged in the feces when the insect takes a subsequent blood meal. Transmissions to a new mammalian host occurs when the infective metacyclic trypomastigotes contaminate mucous membranes, conjunctivas, or breaks in the skin and invade a variety of host cell types. Once inside the cell, they transform into amastigotes and multiply intracellularly. They eventually cause cell rupture with release of parasites, invade adjacent cells, spread via the lymphatics and bloodstream to distant sites, and initiate subsequent multiplicative cycles. Transmission has also been shown to occur by blood transfusions and organ transplants, transplacentally, and by accidental inoculation in the laboratory [11].

In the naturally acquired infection, a chagoma may appear at the site of entry. If the portal of entry is the conjunctiva, the patient may develop painless unilateral periorbital edema termed the Romaña's sign [11]. Dissemination of the parasite may be accompanied by fever, malaise, edema of the extremities and face, morbilliform rash, generalized lymphadenopathy, and hepatosplenomegaly. If heavy tissue parasitism occurs, clinically significant myocarditis may ensue in a small proportion of patients occasionally leading to congestive heart failure and death. Life threatening arrhythmias, typical of chronic cardiac Chagas' disease, usually do not occur in acute Chagas' disease. Amastigotes may parasitize cells of the gray and white matter of the central nervous system in acute infection and cause meningoencephalitis, especially in young children. When this occurs, it is usually in conjunction with acute myocarditis and is associated with a very poor prognosis. The signs and symptoms of acute Chagas' disease usually abate within 4–8 weeks. They then enter the indeterminate phase in which the parasite is contained by the host's immune system or is sequestered in intracellular spaces protected from destruction. This phase is characterized by the lack of overt symptoms, detectable antibodies to *T. cruzi*, and subclinical parasitemia [11].

Chronic Chagas' disease may become clinically evident years or decades after the initial infection. Symptoms develop in only 10–30% of chronically infected persons, with cardiac manifestations as the predominant findings [11]. Congestive heart failure, arrhythmias, thrombosis, dizziness and syncope are typical findings. However, seizures are rare in chronic Chagas' disease, unless related to a thrombo-embolic event. Although there have been disagreements concerning the pathogenic basis of chronic chagasic cardiomyopathy; persistence of parasites, autoimmunity, and microvascular dysfunction have all been cited as etiologic factors leading to progressive organ

dysfunction. The cardiomyopathy develops insidiously often affecting the right ventricle preferentially. Once congestive heart failure ensues, life expectancy is limited. The gastrointestinal tract is also frequently affected in chronic Chagas' disease. Megaesophagus is the most common clinical expression with symptoms similar to that of idiopathic achalasia such as chest pain, dysphagia, odynophagia, cough, and regurgitation. Hypersalivation, parotid enlargement, and repeated aspiration may also occur. Constipation and abdominal pain are the typical symptoms of patients with megacolon. In patients with advanced megacolon, obstruction, perforation, and sepsis may develop.

Although the incidence of reactivation of Chagas' disease in the setting of immunosuppression is unknown, it often follows a more severe clinical course than the Chagas' disease in an immunocompetent person [7]. Reactivation of Chagas' disease has been described in patients with leukemia, and with kidney and heart transplantation. While central nervous system involvement has not been described in chronic Chagas' disease in immunocompetent patients, it is a common presentation of reactivation of Chagas' disease acquired years prior to the onset of immunosuppression [12-16].

Chagas' disease and AIDS

Chagas' disease/HIV co-infection has been well described in the literature [5] since the initial report by del Castillo et al [13]. In 1990, Del Castillo and colleagues reported the first clinical observation of Chagas' disease and AIDS. They described the case of a 19-year old man with hemophilia B who presented with fever, headaches, photophobia, and weight loss. A CT scan of the brain revealed a large hypodense lesion comprising the right frontal lobe with mass effect and herniation. Suspecting a glioma, the patient underwent an emergent neurosurgical resection of the lesion. Subsequent pathologic examination revealed inflammatory perivascular infiltrates and clusters of *T. cruzi* amastigotes. Chagas' and HIV-1 serology were both positive and the CD4 cell count was low. He was treated with nifurtimox for 4 weeks with stabilization of his neurologic symptoms. However the patient's clinical course was complicated by acute myocarditis and he later died of respiratory failure [13]. This clinical presentation highlights several key aspects concerning the presentation of Chagas' disease in AIDS. The central nervous system is the most commonly affected site, occurring in roughly 75% of cases [13,15,16]. Space occupying lesions are commonly seen with Chagas' disease in AIDS. The classic manifestations are that of an acute meningoencephalitis, with fever, headaches, seizures, vomiting, and focal neurological deficits. Examination of the cerebrospinal fluid may show mild pleocytosis with lymphocyte predominance, increased protein, and the presence of *T. cruzi* trypomastigotes [4,13,15,16]. These findings are typical for acute Chagas' disease in the immunocompetent as well as for reactivated Chagas' disease in the immunocompromised. Brain imaging by CT scan often reveals a single or multiple hypodense subcortical lesions with or without enhancement. The lesions predominantly involve the white matter of the brain. Histopathologic examination reveals severe inflammation associated with numerous amastigotes parasitizing glial cells and occasionally neurons [17]. Although central nervous system *Toxoplamsa gondii* infection in AIDS patients involves the basal ganglia and thalamus more commonly, the lesions of central nervous system Chagas' disease are often mistakenly attributed to this parasite as well as other opportunistic infections. This lack of specificity of brain imaging and the broad differential of space occupying lesions in individuals with AIDS underscore the usefulness of a brain biopsy to affect accurate diagnosis and appropriate therapy.

The heart is the next most commonly affected organ recognized in 25% to 44% of cases [11]. Myocarditis as the singular manifestation of Chagas' disease in HIV-infected patients is uncommon. It is usually associated with central nervous system involvement and is diagnosed clinically or at autopsy [11,17]. Findings from necropsy studies suggest that a significant proportion of Chagas' disease in HIV/AIDS have clinically silent cardiac disease despite brisk inflammation with nests of parasites in the myocardium [17]. Clinical manifestations are those of heart failure and arrhythmias. Another key aspect found in HIV-infected patients who present with clinically symptomatic Chagas' disease is that of significant immunosuppression. Chagas' disease in HIV infected patients has been predominantly described in those with advanced disease with CD4 counts below 200 cells/ml [3,4,13,15,16].

The histopathology of the central nervous system and the heart associated with reactivated Chagas' disease in AIDS has been well described [3,8,17]. The brain is grossly enlarged in size and weight with scattered areas of softening and hemorrhage. The white matter appears to be more involved than the gray matter. Microscopically, meningoencephalitis with necrosis and hemorrhage are found in the scattered areas of softening. Meningitis is present in varying degrees of intensity. Macrophages and lymphocytes account for the majority of the inflammatory infiltrate noted in the parenchyma and perivascular spaces, followed by plasma cells and granulocytes. Microglial nodules and disseminated multifocal astrocytic gliosis of the white matter are invariable found in most of the cases. Heavy parasitism is noted in glial cells and in areas of necrosis and hemorrhage. Parasites are also found in macrophages, around blood vessels, free in intercellular spaces but rarely in neuronal cells [3,17]. The findings in the myocardium vary with the intensity of the inflamma-

tion provoked by *T. cruzi* parasitism. The myocarditis may be mild with limited focal, intrafascicular or endomysial infiltrates with macrophages and lymphocytes or it may be more severe with extensive and more widespread foci of inflammatory infiltrates. The inflammatory process has been observed in every layer, from the endocardium to the epicardium. Often the inflammatory cells can be seen dissecting one myocardial cell from another. Another feature of cardiac involvement is the proliferation of connective tissue, which may be diffuse with several areas connected by bridging fibrous fascicles [11,17,18]. Although the precise mechanisms that drive the pathogenesis of Chagas' disease have not been fully defined, clinical studies and experimental models suggest that the severity of tissue parasitism during acute disease correlates with the symptomatic and pathologic findings in chronic reactivated disease.

As more cases have been reported, we have gained a better understanding of the interaction between *T. cruzi* and HIV during coinfection. Upon review of the case reports and case series of investigators such as Ferreira and Sartori from Brazil, it appears that the clinical manifestations of Chagas' disease in the HIV-infected represent reactivation and not primary infection with *T. cruzi* [4,7,13,15,19]. This is similar to *T. gondii*, which is regarded by some as the prototypical opportunistic infection, which is acquired years prior to presentation, remains in latency for an indeterminate time, and only reactivates in the setting of AIDS to cause symptoms and disease. The cases of Chagas' disease and HIV infection that have been reported are described in patients presenting to tertiary care hospitals situated in urban centers. Although Chagas' disease may be endemic in these urban areas, vector-borne transmission usually does not occur there. The typical epidemiologic sequence of events is for patients to acquire *T. cruzi* infections while residing in rural areas of endemicity, to move to urban areas where they acquire HIV infection, and to present clinically as immunosuppression ensues and *T. cruzi* reactivates [3,13,15,16,19].

The level of parasitemia observed in HIV infected individuals with symptoms of Chagas' disease is useful in diagnosis [2,20]. Direct microscopic examination of blood and cerebrospinal fluid may reveal *T. cruzi* trypomastigotes [20]. This finding may precede the clinical manifestations of disease or it may be discovered with the onset of symptoms. Studies by Perez Ramirez and Sartori demonstrate that HIV-infection lead to a substantial increase of *T. cruzi* parasitemia in patients with Chagas' disease [4,7,21]. Moreover, the reactivation of Chagas' disease and its subsequent parasitemia has been shown to be associated with an increase in plasma HIV-1 viral load [4]. Other studies have shown an increased frequency of detection of *T. cruzi* parasitemia in HIV-seropositive subjects with chronic Chagas' disease than in HIV-seronegative subjects, a higher level of parasitemia as established by xenodiagnosis, and a higher level of parasitemia in AIDS than in less advanced HIV infection [19]. Importantly, mice coinfected with murine leukemia virus, which causes immunodeficiency, and *T. cruzi* have greater parasitemia, and myocardial parasitism with inflammation than do mice infected with *T. cruzi* alone [22].

HIV-infected individuals have defects in cell-mediated immunity including decreased lymphocyte proliferation and decreased production of IL-12 and IFN-γ, which are often associated with progression of HIV infection. These deficiencies are among the contributory factors leading to opportunistic infection and may appear prior to CD4+T-cell depletion. It has recently been demonstrated that CD154, a molecule expressed on activated CD4+ T cells is important in the regulation of both cell mediated and humoral immunity and critical for the resistance to opportunistic infections. In CD4+ T cells from HIV infected patients the expression of CD154 was impaired in response to a number of pathogens including *T. gondii*. There was a correlation with decreased production of IL-12 and IFN-γ in response to Toxoplasma [23]. These observations could be applicable to *T. cruzi*. Various studies point to the crucial role of cytokines such as interferon (IFN)-γ, tumor necrosis factor (TNF)-α, interleukin (IL)-12, and nitric oxide in host resistance and susceptibility in *T. cruzi* infection [6]. IFN-γ and TNF-α have been implicated in the activation of macrophages during the acute phase of the infection [4,6]. These two cytokines induce high levels of nitric oxide, which may contribute to the control of parasite replication. Mice deficient in IFN-γ have higher parasitemia and myocardial parasitism but lower myocardial inflammation and earlier mortality. In contrast, mice deficient in IL-12 have milder parasitemia and myocardial parasitism but greater myocardial inflammation and later mortality. Michailowsky and colleagues have described the role of cytokines in tissue parasitism. In a series of experiments with mice, expression of IL-12 and IFN-γ has been shown to increase susceptibility to the Colombian strain of *T. cruzi*. In contrast, IL-4 expression has been associated with lower parasitemia and mortality [6].

Earlier studies have postulated a correlation between genetic diversity in *T. cruzi* and variability in clinical disease [21,24]. Murine models have demonstrated the different tissue tropism of *T. cruzi* as illustrated by the Colombian strain's affinity for the heart and brain [6]. In reactivated Chagas' disease and HIV coinfection, several strains of *T. cruzi* may be discovered through genetic and phylogenetic testing in any given patient. Studies by Pacheco and Perez-Ramirez have not found a correlation between a particular genotype and the reactivation of

Chagas' disease in HIV-seropositive patients [21,24]. On the other hand, Marques de Brito has demonstrated that mice infected with a particular genotypic strain express a genetically divergent strain after immunosuppression [25]. However, current evidence does not support a clear link between genetic variability and clinical disease in humans.

The treatment of acute *T. cruzi* infection is with Benznidazole or Nifurtimox. The usual dosing regimen for Benznidazole is 5–7 mg/kg per day in 2 divided doses for 30–90 days. The usual dosing regimen for Nifurtimox is 8–10 mg/kg per day in 3–4 divided doses for 90–120 days. However, the duration of therapy has not been studied in HIV/AIDS, but in the absence of immune reconstitution chronic suppressive therapy would likely be required. In a somewhat analogous situation, many patients with Chagas' disease undergoing organ transplantation have required therapy during the period of immunosuppression.

Summary

We have attempted to highlight some of the knowledge gained in the decade following the first description of Chagas' disease in the HIV-seropositive population. Now well recognized as an opportunistic infection in AIDS, more cases can be expected given the confluence of certain demographic and epidemiologic trends. Chagas' disease is widely distributed in Central and South America affecting 18 million people in 21 different countries [2,11]. As this population overlaps and intersects with the growing HIV-seropositive population, the incidence of disease is likely to increase. Moreover as persons continue to migrate from endemic areas, the potential for new cases in the United States, Canada and Europe will also increase. Clinicians and researchers will have to consider the risk of reactivation of latent *T. cruzi* infection in their approach toward immunocompromised patients with relevant exposures. This is particularly important when one considers that the efficacy of specific anti-parasitic drug therapy has not been evaluated in the setting of HIV/AIDS in a systematic manner.

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