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Case Report

Dengue fever and human T-cell lymphotropic virus type 1 infection

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SUMMARY

Globalization has increased both the number of emergent diseases and the diversity of co-infections, which could in turn mutually influence the pathogenesis of well-known infectious diseases. Here, we report the first series of chronic human T-cell lymphotropic virus type 1 (HTLV-1) patients co-infected with the dengue fever virus. As both of these diseases are immuno-mediated, we anticipated interference in the development of both diseases, with atypical clinical and laboratory parameter results. All the patients had classic dengue fever, and the main outstanding abnormality was leukopenia associated with lymphopenia. Although a mutual influence was expected, dengue fever did not affect the clinical course of HTLV-1 infection, and HTLV-1 proviral loads revealed unpredictable patterns of change.

1. Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) is the etiologic agent of a slowly progressive neurodegenerative disease named HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), and infects mainly CD4+ T-cells. In HAM/TSP patients, activated T-cells migrate into the central nervous system after blood–brain barrier breakdown induced by proinflammatory cytokines,[1] which are also involved in tissue damage related to disease development.[2,3] It has also been claimed that dengue fever is an immunopathological disease, with patients initially presenting fever, retro-orbital headache, severe myalgia, and rash.[4] Thereafter, some individuals can rapidly develop dengue hemorrhagic fever, which is characterized by thrombocytopenia, diffuse capillary leakage, hemoconcentration, and hypotension, which may be followed by hemorrhage. Monocytes/macrophages are considered target cells for dengue infection, acting as antigen-presenting cells and secrete cytokines that participate in T-cell activation[5] and in the control of endothelium permeability.[6] Therefore, the pathophysiological mechanisms observed in HTLV-1 infection and dengue fever could induce clinical and laboratory changes in the course of each disease, such as alterations in HTLV-1 proviral load (PVL), which is associated with HAM/TSP progression,[7] and/or more severe clinical manifestations of dengue fever. The impact of pathogens, such as hepatitis C virus[8] and *Strongyloides stercoralis*,[9] on the evolution of HTLV-associated diseases has been subject of studies. Pathogen–host interactions in co-infected individuals have been reported to be associated with a dysfunctional cell immune response and disease severity.

The Instituto de Pesquisa Clínica Evandro Chagas/Fundação Oswaldo Cruz (IPEC/FIOCRUZ) is a reference center for acute febrile diseases and neuroinfections, particularly HTLV-1 infection, with a cohort of 505 patients. In view of the paucity of data in the medical literature concerning co-infections in patients with HTLV-1, we describe here the main clinical and laboratory manifestations of this series of cases.

2. Methods

During the 2011 dengue epidemic in Rio de Janeiro, Brazil, characterized by circulation of the four dengue virus (DENV) serotypes with predominance of serotype 1, four HTLV-1-infected patients followed in the IPEC/FIOCRUZ cohort were admitted with a suspicion of dengue infection. Peripheral blood samples from all patients were submitted to reverse transcription PCR (RT-PCR) for the detection and typing of DENV[10] and screening of DENV-specific

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Table 1
Dengue fever in HTLV-1 patients: main clinical and laboratory data

	Age (years)	Gender	Dengue classification	HTLV-1-associated disease	EDSS progression	Lower leukocyte count ($\times 10^9$/l)	Platelet count ($\times 10^9$/l)	HTLV PVL before DF (%)	HTLV PVL after DF (%)
Case 1[a]	50	M	DF	AC	No	2.30	76	ND	ND
Case 2	60	F	DF	HAM/TSP	No	1.92	188	11.01	16.32
Case 3	49	M	DF	Polymyositis	No	2.91	201	4.64	4.73
Case 4	56	F	DF	HAM/TSP	No	3.11	161	5.12	3.10

AC, asymptomatic carrier; DF, dengue fever; EDSS, Expanded Disability Status Scale; F, female; HAM/TSP, HTLV-1-associated myelopathy/tropical spastic paraparesis; HTLV-1, human T-cell lymphotropic virus type 1; M, male; ND, not detectable (<1 infected cell in 10^4 peripheral blood leukocytes); PVL, proviral load.
[a] HIV co-infected.

IgM (PanBio Dengue IgM capture ELISA, Inverness Medical, Australia). Clinical and laboratory data are summarized in Table 1, and include: leukocyte and platelet counts, HTLV-1 PVL measured as a percentage of infected cells in peripheral blood leukocytes (PBL) before and after dengue fever, and score on the Expanded Disability Status Scale (EDSS)[11] employed to evaluate the clinical progression of HAM/TSP. Written informed consent was obtained from the patients for publication of this case series report.

3. Results and case reports

All patients were positive for the presence of DENV-specific IgM and for DENV-1 by RT-PCR (except case 4). There was no evidence of hemoconcentration or bleeding, and the serum albumin levels remained normal in all cases. The four patients presented classic dengue fever, accompanied by leukopenia, and the EDSS score remained unaltered even though the four patients had different clinical manifestations of HTLV-1 infection (Table 1).

3.1. Case 1

A 50-year-old man was admitted to the hospital with fever, headache, and retro-orbital pain. He had leukopenia with lymphocytosis and thrombocytopenia (platelet count 76×10^9/l), and was hospitalized for 4 days because of neutropenia (cell count 1.54×10^9/l). This patient was HIV co-infected but asymptomatic for both retroviral infections. Before the onset of dengue fever, his CD4 cell count was higher than 1000 cells/mm^3; His HIV viral load (VL) was below 50 copies/mm^3, and HTLV-1 PVL was undetectable. During and after dengue fever, his clinical condition in association with the HTLV-1 and HIV infections remained unaltered. After dengue fever, he maintained high levels of CD4 lymphocytes (939 cells/mm^3), and HTLV-1 PVL and HIV VL both remained undetectable.

3.2. Case 2

A 60-year-old woman was admitted with fever, headache, retro-orbital pain, prostration, myalgia, arthralgia, and vomiting that began the day before admission. Her total leukocyte count decreased from 6.3×10^9/l (day 2) to 1.92×10^9/l (day 4), but the platelet counts remained normal. This patient had a HAM/TSP EDSS score of 7, which remained unaltered. Nevertheless, the PVL increased 48.22% (from 11.01% to 16.32% infected cells/PBL) (Table 1).

3.3. Case 3

A 49-year-old man was admitted with fever, myalgia, and headache. His total leukocyte count decreased from 4.88 to 2.91×10^9/l, and platelet counts remained normal. This patient had HTLV-1-related polymyositis with an EDSS score of 0, which remained unaltered. His HTLV-1 PVL was also unaltered (4.64% to 4.73% infected cells/PBL) (Table 1).

3.4. Case 4

A 56-year-old woman was admitted with fever, headache, retro-orbital pain, and myalgia. She had leukopenia (3.11×10^9/l), but no thrombocytopenia (Table 1). DENV RT-PCR was not performed because blood was collected more than 5 days after disease onset. This patient had HAM/TSP (EDSS score 7) and there were no changes in her neurological condition. Her HTLV-1 PVL decreased 39.5% (from 5.12% to 3.10% infected cells/PBL) (Table 1).

4. Discussion

Despite the small number of cases, this is the first report of dengue fever and HTLV-1 co-infection. The occurrence of dengue fever in HTLV-1 patients could hypothetically influence pathophysiological mechanisms and induce distinct manifestations in the course of HTLV-1 infection. HTLV-1 infects lymphocytes,[7] which are initially depleted during dengue virus infection.[12,13] On the other hand, monocytes/macrophages infected by DENV secrete proinflammatory cytokines that enhance T-cell activation and alter endothelium permeability,[6] which could influence T-cell migration into the central nervous system leading to HAM/TSP progression. The influence of other pathogens on HTLV-1 patient clinical and laboratory profiles can be observed in co-infections, such as *Strongyloides stercoralis*[9] and hepatitis C virus.[8]

However, in this case series, it was observed that this co-infection did not alter the clinical course of either HTLV-1 or dengue infection. All patients presented non-severe classic dengue fever without warning signs, bleeding disorders, or other complications. Among hematological alterations, leukopenia was a common finding in the four patients; this has been associated with dengue infection in other studies.[12]

With regard to neurological status, no patient worsened, as determined by the maintenance of EDSS scores. A variation in the pattern of HTLV-1 PVL quantified before and after dengue fever episodes was also not observed, as described in Table 1. The intra-individual fluctuation observed in the HTLV-1 PVL did not follow a common tendency. Indeed, it was compatible with levels observed during the normal clinical course of HTLV-1 infection, as described by Demontis et al.[14]

Because of the small number of cases reported here, we do not consider this a conclusive study. Nevertheless, despite the expected mutual influence of DENV and HTLV-1 infections in each virus-related disease, all patients presented classic dengue fever and no worsening of HAM/TSP, suggesting that both diseases present independent pathogenic mechanisms.

Conflict of interest: There are no conflicts of interest to declare.

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