Letter to Editor/Carta ao Editor

Atypical lymphocytosis in leptospirosis

Linfocitose atípica na leptospirose

Viroj Wiwanitkit[1]

Dear Editor,

Sir, I read the recent report on atypical lymphocytosis in leptospirosis with a great interest[1]. Damasco et al concluded that *atypical leukocyte subsets are associated with partial protection during the disease course of leptospirosis*"[1]. Some points should be discussed. First, as a nature of retrospective study, there can be many pitfalls. The detection of atypical lymphocytosis is usually problematic if there is no expert medical technologist control the quality of analysis[2]. For sure, the retrospective study cannot control the quality of the laboratory analysis. Second, as Damasco et al mentioned, several diseases can mimic leptospirosis. An important disease that can present atypical lymphocytosis is dengue infection. This infection is also common in the studied setting. The question is whether the diagnosis of leptospirosis is correct. Also, the co-infection between leptospirosis and dengue can be possible[3] and this cannot be ruled out in this work.

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Article/Artigo

Atypical lymphocytosis in leptospirosis: a cohort of hospitalized cases between 1996 and 2009 in State of Rio de Janeiro, Brazil

Linfócitos atípicos na leptospirose: coorte de pacientes hospitalizados entre 1996 e 2009, Estado do Rio de Janeiro

Paulo Vieira Damasco [1], Carlos André Lins Ávila [1], Angélica Täpia Barbosa [1], Marilza de Moura Ribeiro-Carvalho[2], Geraldo Moura Batista Pereira [2,3], Elba Regina Sampaio de Lemos[4], Márcio Neves Bóia [1] and Martha Maria Pereira[5]

ABSTRACT

Introduction: Leptospirosis is a zoonotic disease found in tropical and temperate countries, and its clinical diagnostic confusion with arboviruses (dengue fever, oropouche fever and yellow fever), Brazilian spotted fever, viral hepatitis and hantaviruses has been an ongoing public health concern. The aim of this observational study was to demonstrate an association between findings of atypical lymphocytosis and the progression of endemic leptospirosis. **Methods**: A retrospective analysis was performed on the demographic, epidemiological, clinical and laboratory aspects of 27 human leptospirosis cases that occurred over a period of 13 years (1996-2009) with no reported epidemic outbreaks in Rio de Janeiro, Brazil. **Results**: The overall mortality rate was 11.1% in our cohort of hospitalized cases. However, there was no mortality among patients with atypical lymphocytosis (OR = 11.1; 95% CI = 1.12-110.9; p = 0.04). Two patients who were in the septicemic phase showed signs of expansion of γδ T cell responses in peripheral blood. **Conclusions**: Atypical lymphocytosis may be observed in patients with leptospirosis. Our observations suggest that these atypical leukocyte subsets are associated with partial protection during the disease course of leptospirosis.

Keywords: Leptospirosis. Atypical lymphocytes. γδ+ T cells. Clinical features.

RESUMO

Introdução: Leptospirose é uma zoonose que permanece endêmica em regiões tropicais e temperadas. A dificuldade no diagnóstico clínico diferencial entre os quadros de leptospirose humana e as várias arboviroses (dengue, febre amarela, febre de oropouche), febre maculosa brasileira, hepatite viral e hantavirose permanece um problema na Saúde Pública. **Métodos**: No presente estudo, foi realizada análise retrospectiva de características demográficas, epidemiológicas, clínicas e laboratoriais de 27 casos de leptospirose humana que ocorrerem durante um período de 13 anos sem ocorrência de notificação de surtos epidêmicos no Rio de Janeiro, Brasil (1996-2009). **Resultados**: A mortalidade da coorte de pacientes com leptospirose correspondeu a 11,1%, sem embargo, o grupo de pacientes com atipia linfocitária não evoluiu para o óbito (OR = 11,1; 95% CI = 1,12-110,9; p = 0.04). Em duas oportunidades, foi observada uma expansão dos linfócitos T gama-delta no sangue periférico de pacientes na fase septicêmica da leptospirose. **Conclusões**: Atipia linfocitária pode ocorrer em pacientes com leptospirose. Nossos dados também sugerem que os linfócitos atípicos podem estar envolvidos na patogênese da leptospirose.

Palavras-chaves: Leptospirose. Linfócitos atípicos. Linfócitos gama-delta. Características clínicas.

1. Disciplina de Doenças Infecciosas e Parasitárias, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ. 2. Laboratório de Imunopatologia, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ. 3. Laboratório de Microbiologia, Fundação Oswaldo Cruz, Rio de Janeiro, RJ. 4. Laboratório de Hantaviroses e Rickettioses, Fundação Oswaldo Cruz, Rio de Janeiro, RJ. 5. Laboratório de Referência Nacional para Leptospirose, Centro Colaborador da Organização Mundial da Saúde, Fundação Oswaldo Cruz, Rio de Janeiro, RJ.

Adddress to: Dr. Paulo Vieira Damasco. DIP/FCM/HUPE/UERJ. AvProfessor Manoel de Abreu 444/ 2ª andar - Vila Isabel, 20550-170 Rio de Janeiro, RJ, Brasil.
Fax: 55 21 2587-6323
e-mail: damascopv@ig.com.br

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INTRODUCTION

Leptospirosis is a zoonosis that is caused by infection with pathogenic *Leptospira* species. This disease is found worldwide in both temperate and tropical climates but its major health impacts have been underestimated in developing countries[1]; additionally, the disease has only recently been recognized as an emerging infectious disease[2]. Transmission from animal carriers to humans results from exposure to the urine of infected animals, either by direct contact or more frequently, through contaminated soil or water. The lack of a simple and reliable laboratory test, however, remains the major barrier for diagnosis and epidemiologic surveillance[1-3]. A diagnosis may be made on the basis of the clinical presentation and symptoms that show characteristics of the severe disease form together with a suggestive epidemiological history[3,4]. However, a clinical diagnosis of leptospirosis is often inaccurate because the disease shares clinical features with a range of other infectious diseases[5-8]. Some of these other viral and bacterial infections, including some arboviruses (e.g., dengue fever, Oropouche fever and yellow fever), Brazilian spotted fever, viral hepatitis and hantaviruses, are matters of public health concern in tropical countries and may be related to the misdiagnosis of leptospirosis[9,10]. In one study in Thailand, the positive predictive accuracy of a hospital-based diagnosis of leptospirosis in nine provinces was low, with only 143 out of 700 (20%) suspected cases being confirmed by laboratory testing. The causes of illness in the remaining 80% of cases were not found[3]. Furthermore, routine laboratory data are generally nonspecific; either a normal differential white blood cell count or a predominance of polymorphonuclear leucocytes is generally seen in leptospirosis cases. Peripheral lymphocytosis with the presence of circulating atypical lymphocytes is not described

1. Wiwanitkit House, Bangkhae, Bangkok, Thailand.
Address to: Dr. Viroj Wiwanitkit. Wiwanitkit House, Bangkhae, 10160 Bangkok Thailand.
Phone: 668 7097-0933
email: somsriwiwan@hotmail.com

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Resposta dos autores: Linfócitos atípicos na leptospirose: coorte de pacientes hospitalizados entre 1996 e 2009, no Estado do Rio de Janeiro, Brasil

Paulo Vieira Damasco[1], Carlos André Lins Ávila[1], Angélica Tápia Barbosa[1], Marilza de Moura Ribeiro Carvalho[2], Geraldo Moura Batista Pereira[2,3], Elba Regina Sampaio de Lemos[4], Márcio Neves Bóia[1] and Martha Maria Pereira[5]

Dear Editor,

We thank Prof. Wiwanitkit for his critical evaluation and comments. We agree with the observation that there are limitations in retrospective studies. However, we must clarify some aspects regarding the main issues raised. As a routine procedure, the protocols for laboratorial confirmation of clinical suspicions involve collaboration with the department of hematology at the same university and three reference laboratories accredited by the Ministry of Health, Brazil. The reference laboratories for leptospirosis, dengue, hantavirus, and ricketsiosis are located at the *Instituto Oswaldo Cruz*, *Fundação Oswaldo Cruz* (IOC/FIOCRUZ), Rio de Janeiro. All laboratories involved comply with standards of quality management procedures. The above-mentioned accreditations, protocols, and partnerships already existed at the time in which the patients were examined, diagnosed, and treated-although in retrospect regarding the analysis of the published data in this paper. The criterion to consider the presence of morphologically atypical lymphocytes was the observation of enlarged lymphocytes with abundant cytoplasm, vacuoles, and indentations of the cell membrane. The main serological test for leptospirosis was the microscopic agglutination test (MAT), considered to be the gold standard in the World Health Organization/International Leptospirosis Society guidelines, 2003. The MAT and polymerase chain reaction tests were performed in the national reference laboratory for leptospirosis in Brazil. A total of 14 of 27 cases were simultaneously tested for dengue, hantavirus, spotted fever group, and rickettsia when these diagnostic possibilities were considered at the first clinical presentation. The results were negative for those infections and positive for leptospirosis. Although the occurrence of dengue and leptospirosis is an important epidemiological aspect in the region, the concomitant infection in individual cases is considered to be rare or uncommon. It seems to be also true as a general picture considering the available data of the international literature. It should be stressed that the two cases with increased frequency of γδ T-lymphocytes were positive for leptospirosis showing negative results to the dengue fever tests. We believe the additional information is sufficient to answer questions about the diagnosis. The manuscript does not state categorically the possibilities or predictions, but it raises a hypothesis that is well grounded in reliable data, to be confirmed by further prospective studies.

1. Disciplina de Doenças Infecciosas e Parasitárias, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ. 2. Laboratório de Imunopatologia, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ. 3. Laboratório de Microbiologia, Fundação Oswaldo Cruz, Rio de Janeiro, RJ. 4. Laboratório de Hantaviroses e Rickettioses, Fundação Oswaldo Cruz, Rio de Janeiro, RJ. 5. Laboratório de Referência Nacional para Leptospirose, Centro Colaborador da Organização Mundial da Saúde, Fundação Oswaldo Cruz, Rio de Janeiro, RJ

Address to: Dr. Paulo Vieira Damasco. DIP/FCM/HUPE/UERJ. Av. Prof. Manoel de Abreu 444/2º andar, Vila Isabel, 20550-170 Rio de Janeiro, RJ, Brasil.
Fax: 55 21 2587-6323
e-mail: damascopv@ig.com.br
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