Acta Tropica 128 (2013) 1–6

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

Review

Cystic echinococcosis in South Africa: The worst yet to come?

Kerstin Wahlers[a,b], Colin N. Menezes[c], Thomas Romig[d], Peter Kern[b], Martin P. Grobusch[c,e,f,*]

[a] Department I of Internal Medicine, Hospital of the University of Cologne, Kerpener Str. 62, 50937 Cologne, Germany
[b] Comprehensive Infectious Diseases Center, University Hospitals, Albert-Einstein-Allee 23, 89081 Ulm, Germany
[c] Division of Infectious Diseases, Department of Internal Medicine, University of the Witwatersrand, Faculty of Health Sciences, 7 York Road, Johannesburg 2193, South Africa
[d] Parasitology Unit, University of Hohenheim, Emil-Wolff-Str. 34, 70599 Stuttgart, Germany
[e] Institute of Tropical Medicine, University of Tübingen, Wilhelmstraße 27, 72072 Tübingen, Germany
[f] Center of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Division of Internal Medicine, Academic Medical Center, University of Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 17 October 2012
Received in revised form 3 June 2013
Accepted 4 June 2013
Available online 14 June 2013

Keywords:
Cystic echinococcosis
HIV
Tuberculosis
Co-infection
Sub-Saharan Africa

ABSTRACT

A considerable number of cases of cystic echinococcosis (CE) are reported from South Africa, but the exact epidemiology remains unknown. In addition, southern Africa is one of the global regions worst afflicted by an excessively high HIV- and TB co-endemicity. As deductable from anecdotal observation, the immune modulation caused by all three diseases seems to affect the clinical courses of all of them. Due to the ongoing high HIV and TB infection rates and the long latency period of CE, South Africa may experience increasing numbers of CE with potentially unusual and severe clinical courses due to concomitant immune suppression. The extent of the problem and the additional complexity of appropriate patient care remain to be recognized.

Contents

1. Introduction

The epidemiology of cystic echinococcosis (CE) in South Africa is by-and-large unclear and has never been investigated systematically in full detail. Although falling under the group of Neglected (Tropical) Diseases, it is understood to be common, causing considerable burden of disease. Most publications originating from the Republic of South Africa (SA) report on unusual manifestations of CE, and the disease is understood by the authors to be common (reviewed in Wahlers et al., 2012), as supported by one older report by Kayser and colleagues who saw 20 cases per year in a single hospital in the Eastern Cape Province alone (Kayser, 1980). In a first retrospective study into the epidemiology of CE in SA, data from the National Health Laboratory services suggest that annual numbers were steadily increasing over the past 5 years. In addition,

* Corresponding author at: Center of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Division of Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, PO Box 22600, 1100 DD Amsterdam, The Netherlands. Tel.: +31 20 566 4380; fax: +31 20 69 72286.
E-mail address: m.p.grobusch@amc.uva.nl (M.P. Grobusch).

0001-706X/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.actatropica.2013.06.002

patients with positive test results are significantly younger than those with negatives and fall into the same age group as those worst affected by HIV/AIDS (Wahlers et al., 2011).

Sub-Saharan Africa, with Southern Africa in particular, is, on a global scale, amongst the regions worst afflicted by the human immunodeficiency virus (HIV) and tuberculosis (Tb) co-epidemics. SA features prominently here in terms of the dimension of the problem. Although inhabited by only 0.7% of the global population, is it home to 17% of the world's HIV-infected individuals. In 2006, SA ranked fourth in the world with regard to the overall TB case load, behind far more populated countries like China and India (Abdool Karim et al., 2009). Therefore, in SA, infectious diseases of all kinds have to be viewed in the context of these two epidemics. With HIV/AIDS and tuberculosis, the detrimental effects of both diseases on each other in co-infected individuals are well documented and range from an unusual clinical presentation, increased severity and progression of either disease over complex interactions of drugs used to treat both diseases to complications of immune reconstitution syndrome; all of these associated with increased morbidity and mortality (Klautau and Kuschnaroff, 2005; Sharma et al., 2005).

Here we propose an early hypothesis on a potential explanation for the observations on CE made in South Africa.

2. Consise immune-pathology of HIV

The pathogenesis of immunosuppression in HIV infection remains to be fully understood. Several mechanisms seem to contribute to the progressive loss of immune response to bacterial, viral, fungal or parasitic infections in the course of HIV infection.

Hallmark of the immune dysfunction caused by HIV is the gradual destruction of naive and memory CD4+ T-cells. CD4+ T-cell depletion seems to occur by two major mechanisms. One mechanism is apoptosis, which is induced via the Fas-pathway in infected and uninfected CD4+ T-cells. The second mechanism is the syncytium formation, particularly induced by CXCR4-tropic HIV, which induces membrane fusion between adjacent infected and uninfected cells. These syncytia are short-lived and it is believed that this mechanism accelerates the loss of CD4+ T-cells in late stages of disease (Paranjape, 2005). In consequence, with decreasing numbers of CD4+ T-cells the generation of neutralizing antibodies, a cytotoxic T-cell response and the activation and maintenance of effector T-cells progressively deteriorate. Chronic antigen stimulation leads to high levels of immune activation which results in eventual exhaustion of the T-cells and functional immunosuppression of the remaining CD4+ T-cells (Lane, 2010; Simon et al., 2006).

In addition, HIV infection is associated with an overproduction of Th2-type cytokines (IL-4, IL-10) leading to a shift of the immune response from a pro-inflammatory response towards tolerance against foreign antigen (Agarwal et al., 2001; Klein et al., 1997; Yadav et al., 2009). It was demonstrated in vitro that PBMC of HIV-positive donors do not proliferate as well to mitogen or Candida antigen stimulation as those of HIV-negative donors (Hertoghe et al., 2000).

Apart from CD4+ T-cells, other cells of the immune system are infected and affected by HIV; in particular, macrophages and dendritic cells. These cells do not appear to be reduced in numbers, but their function is altered by HIV. In macrophages, the expression of programmed-death 1 (PD-1) and its ligands, which regulate T-cell activation and tolerance, is upregulated. As a consequence, T-cell activation and responses are inhibited (Said et al., 2010). In addition, HIV-infection of macrophages impairs their ability to phagocytize opsonized pathogens (Mazzolini et al., 2010). HIV surface antigens alter the maturation of dendritic cells which appear to be phenotypically mature but are functionally impaired, with reduced antigen uptake capabilities as well as reduced allo-stimulatory activity, which is important for the generation of protective immunity (Fantuzzi et al., 2004).

In summary, HIV-infection leads to a state of impaired recognition and elimination of pathogens and promotes a Th2-dominated environment of tolerance of foreign antigens.

3. Concise immune-pathology of tuberculosis (Tb)

Cellular immunity and T-cell mediated responses in particular are essential to the regulation of the interaction between *Mycobacterium tuberculosis* and the host. Brighenti et al. recently reviewed the current knowledge of immune-pathology of Tb (Brighenti and Andersson, 2012). Protective immunity against Tb depends on CD4+ T-cells producing IFN-γ, TNF-α and effector molecules like perforin, granzymes and granulysin of cytolytic effector T-cells. The innate and adaptive effector functions are regulated by a network of cells and immune-mediators that are modulated by Tb-specific virulence factors. T-cells are recruited to the site of infection by macrophages that fail to eliminate *M. tuberculosis* and chronic infection, and granuloma formation occurs.

In Tb the onset of adaptive immunity is delayed compared to other infections, allowing the bacterial load in the lung to expand significantly. Apoptosis of infected macrophages is inhibited leading to a delayed T-cell response, thereby reducing the presentation of Tb-antigens to bystander cells with subsequent impaired priming of T-cells. In addition, early induction of regulatory T-cells delays effector T-cell responses in the lung. Induction of suppressive immune-regulatory pathways including excessive Th2 responses disturbs host immunity resulting in progressive infection.

M. tuberculosis is capable of surviving in dendritic cells (DC), promoting dissemination of infection. In addition, mycobacterial infection of DC down-regulates their pro-inflammatory activity and antigen-presenting function and leads to a concurrent induction of anti-inflammatory cytokines, impairing adaptive immunity to *M. tuberculosis* (Jiao et al., 2002).

In summary, *M. tuberculosis* leads to a state of impaired antigen-presentation, excessive Th2- and delayed effector T-cell responses to foreign antigen.

4. Concise immune-pathology of helminths

Helminths are capable of secreting immune-modulatory molecules, that affect the host's immune response in a way to suppress protective functions by the induction of innate and adaptive regulatory cells, anti-inflammatory cytokines and specific inhibitory antibody isotypes in order to ensure lifelong persistence of the parasite in the host (Danilowicz-Luebert et al., 2011). CD4+ T-cells are the principle cellular mediators of host–parasite interactions in human helminthic infections. In early infection the differentiation into the different lineages of T-cells (e.g. Th1, Th2, Th17) is driven by antigen-presenting cells, but later in chronic infection cytokine-mediated cross-regulation between T-cell subsets is of increasing importance (Bourke et al., 2011).

Two immunological features are believed to be common in helminth infections. Firstly, the polarisation of CD4+ T-cells towards a Th2 phenotype, which is associated with the production of IL-4, IL-5, IL-9, IL-10 and IL-13, the secretion of IgE and IgG4 by plasma cells and the activation of effector cells. Secondly, an immunosuppression of generalized and helminth-specific immune response is believed to occur regularly (Bourke et al., 2011). As antigen-presenting cells, dendritic cells (DC) are the driving force of Th2 induction in helminth infections. It could be demonstrated that in the presence of helminth infections a specific DC phenotype develops and that DC only mature selectively or show impaired