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A RISK OF VISCERAL LEISHMANIASIS IN CASE OF HELMINTHS CO-INFECTION IN ENDEMIC REGIONS.

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ABSTRACT

People in the endemic region are more prone to helminth infections due to the poor hygienic conditions and their genetic susceptibility may be a factor for *Leishmania* infection. The acute worm infections may not cause fatal outcome to host but it may facilitates the infection of other intracellular pathogens which cause higher rate of morbidity. In case of *Leishmania donovani* infection, helminth infections mainly elicit Th2 type protective host immune response characterized by secretion of IL-4, IL-13, IL-5, IL-9 and IL-10, which may suppress the Th1 protective host immune response. Pre-immune polarized (Th2/Th1) individuals due to the helminth infections and their recovery from infection after treatment may have higher levels of serum IL-4 and IL-13 are highly susceptible for visceral leishmaniasis in endemic regions. These Th2 type cytokines, IL-4, IL-13 and IL-10 have immunosuppressive activity, help in the parasite survival by inhibiting the macrophage induced IFN-γ production and oxidative burst mechanism, thereby enhancing disease progression in chronic visceral leishmaniasis. In addition, IL-5 dependent eosinophilia in helminth infections may cause inflammation in visceral organs leading to tissue damage hence these individuals might be susceptible for parasite attack. Therefore, we hypothesize that the Th2 type cytokine milieu of helminth infection might be increase rate of susceptibility to VL occurrence in endemic regions.

INTRODUCTION

Billions of people and their domesticated animals worldwide are constantly affected by the parasitic helminths, or worms, which come under a diverse group of metazoan organisms [1] causing great morbidity, increased susceptibility to other infectious agents and, in some cases, it may leads to death. Majority of individuals infected with parasitic worms are usually asymptomatic or less symptoms compared to those infected with acute viral or bacterial infections and very few will have life-threatening consequences. Good hygienic conditions and health care can minimize the helminthic parasite infections, but in endemic regions immunological intervention can be an effective option of treatment. Till date, there have been no vaccines or other effective immunotherapies for helminth infections and the understanding of the immune response to these important pathogens remains at a very early stage.

Visceral leishmaniasis (VL), also known as kala-azar, black fever, and Dumdum fever [2], is the most severe form of leishmaniasis. It is the second-largest parasitic killer in the world (after malaria), responsible for an estimated 500,000 cases each year worldwide, with 90% of cases caused by the transmission of *Leishmania donovani* in India, Sudan, Nepal, and Bangladesh. [3]. Every year, more than 100,000 cases of VL occur in India alone and in the state of Bihar accounting for more than 90% of these cases, followed by West Bengal and Eastern Uttar Pradesh [5]. It is endemic in 88 countries of the world including tropics, sub-tropics and the Mediterranean basin (WHO, 1984) among which 16 are developed countries and 72 are developing countries. The parasite migrates to the internal organs such as liver, spleen (hence '*visceral*') and bone marrow without causing clinical symptoms [4].

Host immune response to helminth infection

The primary cause of disease in many helminth infections is due to the under development of immune system after encountering the pathogens which lives longer and causes chronic infections. Helminth pathogens differ based on the presence of different glycoconjugates, which contain unusual sugars [15, 21, 24], thought play a role in Th2 response development [22]. These features of helminth Ag are likely to be recognized by Toll receptors and/or other pattern recognition receptors [6]. This extensive organismal complexity, in the majority of cases evokes Th2-like immune response against the worms with the production of a significant quantity of IL-4, IL-5, IL-9, IL-10, and IL-13 and thereby developing a strong immunoglobulin E (IgE), eosinophil, and mast cell responses. Among these cytokines, IL-4 and IL-10 may play a crucial role in reducing the severity of acute disease and

allowing the pathogen survival. Thus, a Th2 response contributes to the immunopathology of helminth infections [11], and simultaneously protecting against superinfection. Helminth antigen (Ag) can inhibit dendritic cell migration [7] and their activation that normally would promote IL-12 production [25]. However, reports indicate that dendritic cells also have the ability to induce strong Th2 response without secretion of either IL-4 or IL-12 to helminth Ag's [17, 26]. Helminth infections induced down regulating mechanisms are not yet well known. Although some studies have suggested that helminth antigens activates the host macrophages alternatively (AAMcs) and suppression was mediated by contact-dependent mechanism [16, 18] by the production of NO in response to parasite glycoconjugates [8], or through IL-10 production [19, 23]. However, previous reports have established a role for the Th2 cytokine IL-5, the central regulator of eosinophilia. Eosinophils mediate the parasite killing through antibody-dependent cellular cytotoxicity (ADCC) which emerged as an attractive mechanism for resistance to parasitic worms [10].

Host immune system evasion by helminth parasite

Firstly, parasite evasion is mediated by the primary infection induced host immune response (humoral) may be incapable of killing them due to the antigenic variation, hiding in macrophages, shed parasite membrane bearing immune complexes and by secretion of substances which can digest antibodies but prevents the superinfection by killing the incoming parasite. Helminth worms are in no danger of being phagocytosed and they can remove complement-activating molecules that have attached to their surfaces, or cleave the Fc portion of parasite bound antibodies. Secondly the primary infection causes the anatomical or physiological changes in the host making difficult for incoming parasite to establish infection [27]. In few individuals, after the primary infection the protective Th2 immunity can persist, or fully apparent, following drug clearance making the host resistant to further infection. The parasite infections which induce Th2 pathogenic immune response may be harboring in chronic helminth infections [9, 12, 13, 28]. Evidences are showing that the helminth infection can make individual more susceptible to certain pathogens against which Th1 responses are protective and more resistant to pathogens against which Th2 responses are protective [14, 20].

Immune responses in human VL

The protective host immunity against the *Leishmania* infection is elicited mainly by Th1 type which triggers enhanced leishmanicidal activity by infected macrophages. The key pathological feature of VL is the inability of PBMCs to proliferate or to produce IFN-γ in response to leishmanial antigens [33, 36]. IFN-γ and IL-12 produced by antigen-presenting cells (APCs) and by T cells play a pivotal role in the control of parasite growth and development of host resistance against the parasite [29-35]. Early reports have shown that the Th2 type cytokines (IL-4, IL-5, IL-10, and IL-13) favors the establishment of *Leishmania* infection [37-40]. Chronic infection of *Leishmania* is associated with elevated levels of IL-5, IL-13 and their additive effect can inhibit parasite killing. Moreover, VL pathogenesis have been associated with anti-inflammatory cytokines, IL-4 and/or IL-13 [38, 40-42]. However, protection against VL has been associated with production of multiple proinflammatory cytokines and chemokines, as indicated by the elevated plasma protein levels of IL-1, IL-6, IL-8, IL-12, IL-15, IFN-γ-inducible protein-10 (IP-10), monokine induced by IFN-γ (MIG), IFN-γ and tumor necrosis factor alpha (TNF-α) [38, 43-46]. During the parasite infection to liver, inducing a protective immune response which includes the formation of granuloma and its cytokines such as IFN-γ, IL-12, and low levels of TNF-α contributes to clearance of the parasite [47, 29, 48, 49]. Parasite infection to spleen, pathogenesis is associated with elevated levels of TNF-α and delayed or absence of granuloma formation. In both tissues, susceptibility to *L. donovani* infection is associated with secretion of IL-10. [32, 50]. In human VL, the balance of IFN-γ, IL-12 vs IL-4, IL-10 is critical for the disease outcome [51, 47, 52].

Th1-Th2 bias in co-infection

The Th1-Th2 bipolarization in this circumstance is due to the type of pathogen dominance (intracellular or extracellular). In helminth infection the levels of Th2 cytokines (IL-4, IL-13 and IL-10) are higher and inhibits macrophage derived IFN-γ mediated CD4+ T Cell and dendritic cell activation, which inturn, inhibits the production of IFN-γ, IL-2 and IL-12 respectively (Fig.1). IL-5 causes inflammation in visceral organs, tissue damage and makes them prone to parasite attack. In conclusion, helminth antigens induced Th2 response directly suppressing the protective Th1 response of host against *Leishmania donovani* infection.

Hypothesis

Our hypothesis emphasize that the poor people who are living in low hygienic conditions with malnutrition or contaminated food and water are may be highly susceptible for helminth/VL co-infection. The incidence rate of this co-infection can be mostly seen in children compare to adults. In addition, on the basis of prevalence and reciprocal immune responses of these two parasitic infections in endemic regions, we hypothesized that the VL might be a co-infectious disease in pre-immune polarized healthy endemic individuals who are already infected with helminthic worms.

CONFLICT OF INTEREST

The author has no conflict of interest

GRANT SPONSOR

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Figure. 1 Schematic representation of reciprocal immune response in VL co-infected helminth infection