

Helminths and Autoimmunity: the Good, the Bad and the Ugly

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Autoimmune diseases include a wide range of systemic immune mediated conditions, resulting from a complex interaction between genetic background and multiple environmental factors, such as hormonal and dietary factors, tobacco, vaccines, or infectious agents [1,2]. For almost half a century, infections have been extensively implicated in the pathogenesis of autoimmune diseases and are thought to act as triggers of autoimmune response in genetically susceptible individuals. For example, Epstein-Barr virus (EBV) is strongly suspected to be involved in the occurrence of systemic lupus erythematosus (SLE) and other autoimmune diseases [3]. Parasitic infections, a major cause of human sickness and death worldwide, may also be responsible for induction of autoimmune diseases through several mechanisms, including molecular mimicry of parasitic epitopes, alteration of host antigens, polyclonal activation and expansion of B cell clones generating autoantibodies, and manipulation of the idiotypic network [4,5]. Thus, the sera of patients with chronic parasitic infections, such as malaria, visceral leishmaniasis, shistosomiasis or trichuriasis, were found to contain a wide variety of autoantibodies including anti-

dsDNA, anti-Sm, anti-ribonucleoprotein (RNP), anti-SSA, anti-SSB, anticardiolipin and antineutrophil cytoplasmic antibodies (ANCA). It has been shown that some of the autoantibodies produced under these conditions were directly pathogenic [4,5].

Conversely, in recent decades a new concept has emerged, suggesting a protective role for infections in autoimmune diseases. The “Hygiene Hypothesis,” first proposed by Strachan in 1989 [6], postulates that reduced exposure to microorganisms could be responsible for the recent outbreak of allergic and autoimmune diseases in Western countries. This theory was originally proposed for allergic disorders, claiming that reduced exposure to viruses in childhood may later increase the risk of atopy. Subsequently, it was extended to a wide range of disorders including autoimmune diseases. Indeed, epidemiological data evidenced an inverse relationship between the prevalence of autoimmune disorders and infections, especially parasitic infections. Thus, advances toward greater hygiene and eradication of parasitic infections in industrialized countries would have paradoxically resulted in a higher prevalence of immune mediated conditions. Conversely, endemic areas for parasitic infections have a lower prevalence of autoimmune diseases [7–9]. Supporting this theory, helminths have been found to skew the immune response from a T helper (Th)1 to a Th2 phenotype with increased anti-inflammatory cytokine production, to down-regulate Th17 population while enhancing T and B regulatory cell differentiation [10]. These effects are contrary to pathogenic mechanisms

involved in immune mediated diseases. The beneficial role of helminths was later confirmed by clinical studies of several autoimmune diseases, including multiple sclerosis [11], inflammatory bowel disease [12], rheumatoid arthritis [13], and type-1 diabetes [14], as well as by successfully applying them in experimental models. Various species of helminths were tried and several approaches attempted, namely, i) colonization by helminth larvae, ii) oral administration of helminth eggs, and iii) use of antigens derived from helminths [10]. Helminth-derived therapies were found to prevent or delay the onset and reduce the severity of these autoimmune diseases.

In this issue of *IMAJ*, Zeller et al. [15] report the case of a 35 year old man simultaneously diagnosed with severe SLE and massive infestation by *Taenia solium* (*T. solium*), a pork helminth. According to the authors, this would be contrary to the Hygiene Hypothesis, since helminthic infection did not appear to exert a protective effect against SLE in this patient.

To date, the literature remains sparse regarding the complex relationship between parasites and autoimmune diseases, especially with regard to SLE. It is likely that the effect of parasites depends both on the microorganism involved and the type of disease as well as the genetic background of the host. Within parasitic infections, data on the role of helminths in SLE are lacking. Although the protective role of helminths has been demonstrated in several autoimmune diseases, it is not yet known whether helminths exert a beneficial or a harmful effect in SLE.

Moreover, it is interesting to note that this is the first report of the simultaneous occurrence of *T. solium* infection with an autoimmune disease. No study to date has investigated the effect of *T. solium* on the course of autoimmune diseases.

Despite the lack of specific data on the effect of helminths, in particular *T. solium*, in SLE, it has been demonstrated that infectious agents, including parasites, can trigger autoimmune responses [3,5]. Notably, the presence of anti-dsDNA, anti-Sm and antiphospholipid autoantibodies, all of which may be found in SLE, have been detected in patients with chronic parasitic infections [4,5]. Therefore, in this case, it may be that the helminthic infection contributed to the breakdown of tolerance and the subsequent development of SLE.

Nevertheless, we cannot exclude a beneficial action of *T. solium* infection in this patient. Previous reports suggested a protective effect of some parasites, such as *Toxoplasma gondii* and malarial parasites, in SLE [16,17]. Moreover, pathophysiological mechanisms highlighted in SLE include an excessive differentiation toward Th1/Th17 lymphocytes, resulting in high amounts of pro-inflammatory cytokines, and a marked quantitative and functional deficit in Treg cells [18]. In contrast, helminths are known to inhibit Th1/Th17 response while promoting Th2 and Treg cell differentiation [10]. Thus, it seems reasonable that helminthic infection would have a protective effect in SLE. Indeed, the onset of lupus does not exclude a beneficial effect of the parasite. In the patient described by Zeller et al., *T. solium* infection may have delayed the onset, reduced the severity, or slowed the progression of SLE. In the absence of helminthic infection, the disease was reported to be triggered in patients at a younger age or in a more

severe form. It would have been interesting to know the clinical evolution after *T. solium* eradication, which in this case was precluded by the simultaneous introduction of corticosteroids.

The available data in their report do not allow firm conclusions to be drawn on the role of helminthic infection in the SLE evolution – whether contributing to disease onset or slowing its progression. This case highlights the gap in knowledge on the relationship between parasites and autoimmune diseases. Since infectious agents, especially parasites, have been shown able to promote or prevent autoimmune responses, the target of their action is probably mediated by several factors. Better understanding of these factors could open the way for new preventive and therapeutic strategies. Indeed, we recently successfully employed helminth phosphorylcholine derivatives to treat SLE and colitis models [19,20].

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“Growth for the sake of growth is the ideology of the cancer cell”

Edward Abbey (1927-1989), American author and essayist noted for his advocacy of environmental issues, criticism of public land policies, and anarchist political views

“The successful revolutionary is a statesman, the unsuccessful one a criminal”

Erich Fromm (1900-1980), German social psychologist, psychoanalyst, humanistic philosopher, and democratic socialist. Fromm was associated with the Frankfurt School of critical theory