SOCIEDADE BRASILEIRA DE REUMATOLOGIA

REVISTA BRASILEIRA DE REUMATOLOGIA

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Review article

Intestinal parasites infection: protective effect in rheumatoid arthritis?☆

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ARTICLE INFO

Article history:
Received 16 September 2015
Accepted 3 April 2016
Available online 22 July 2016

Keywords:
Rheumatoid arthritis
Helminth infections
Immunomodulation

ABSTRACT

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease, with a progressive course, characterized by chronic synovitis that may evolve with deformities and functional disability, and whose early treatment minimizes joint damage. Its etiopathogenesis is not fully elucidated but comprises immunologic responses mediated by T helper cells (Th1). An apparent minor severity of RA in patients from regions with lower income could be associated with a higher prevalence of gut parasites, especially helminths. Strictly, a shift in the immune response toward the predominance of T helper cells (Th2), due to the chronic exposure to helminths, could modulate negatively the inflammation in RA patients, resulting in lower severity/joint injury. The interaction between the immunological responses of parasitic helminths in rheumatoid arthritis patients is the purpose of this paper.

Parasitoses intestinais: efeito protetor na artrite reumatoide?

Palavras-chave:
Artrite reumatoide
Parasitoses intestinais
Imunomodulação

RESUMO

A artrite reumatoide (AR) é uma doença inflamatória autoimune, sistêmica, de curso progressivo, caracterizada por exuberante sinovite crônica, que pode gerar deformidades e incapacidade funcional, cujo tratamento precoce minimiza o dano às juntas. Sua etiopatogenia ainda não está completamente elucidada, mas compreende respostas imunológicas com a participação de células T auxiliares (Th1). Uma aparente menor gravidade da AR

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http://dx.doi.org/10.1016/j.rbre.2016.06.004

em pacientes de regiões com menor renda poderia estar associada a maior prevalência de parasitoses intestinais, especialmente as helmintíases. A rigor, um desvio na resposta imune para o predomínio de células T auxiliares (Th2), decorrente da exposição crônica a helmintos, modularia negativamente a inflamação em doentes com AR, e levaria a menor gravidade e dano articular. A revisão de aspectos da influência da reposta imunológica nas parasitoses intestinais, especialmente as helmintíases, em pacientes com artrite reumatoide é o objetivo desse trabalho.

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, systemic inflammatory autoimmune disease characterized by a symmetrical involvement of the synovial membrane of peripheral joints with joint damage and destruction.[1] Its prevalence is estimated at 0.2–1% of the population,[2] predominantly in women and with its highest incidence in the age group of 30–50 years.[1] RA is a multifactorial disease of unknown etiology, for which genetic (HLA-DR1 and HLA-DR4) and environmental (exposure to infections and smoking, among others) factors contribute for the loss of tolerance and organ damage.[3] If not treated properly, the disease can lead to functional limitations, with irreversible deformities and a reduced life expectancy.[1] The impact of RA is significant for both the patient (morbidity and mortality and decreased quality of life) and society (functional impairment with decreased productivity and lower capacity to participate in the labor market).[2]

Intestinal parasites infections include infections caused by protozoa and helminths with high morbidity and mortality. Their prevalence is estimated at 30% of the population of the Americas.[4,5]

Despite the morbidity and, less commonly, mortality that may be associated with parasitic infections, specifically in the case of helminths, subclinical infestations occur, which denounces an adaptation of the host to the parasite, with containment of damage and consequent survival of both sides. This host/parasite adaptation is related to components of the innate immune response and, in the case of the adaptive immune response, to the predominance of a Th2 response, with increased release of the so-called anti-inflammatory cytokines, such as interleukins (IL) 4, 10 and 13.[5]

In the literature, there are reports of lower prevalence and/or severity of RA in populations of sub-Saharan Africa; in our midst, a study conducted in Natal/RN, while addressing patients with systemic lupus erythematosus, found a similar level of severity in lupus patients versus populations of areas of greater economic power.[6] More recently, in a study on children with juvenile idiopathic arthritis cared for at a tertiary center in the state of Ceará, their authors found that about two-thirds of patients could achieve remission using methotrexate and/or leflunomide, despite the prevalence of the polyarticular subtype, which would have a worse prognosis.[7] The delays in establishing the diagnosis and in offering an early treatment, as well as the low family education/income found in our population, are factors considered as capable to aggravate the prognosis in autoimmune diseases. It is curious, therefore, that the long-term progression of these patients is at least equivalent, if not less severe, than that observed in populations with better socioeconomic indicators. This good response in potentially more severe patients, when compared to case series from rich countries of the Northern hemisphere, opens the possibility that environmental factors may be acting in the clinical course of autoimmune diseases.

The aim of this study is to elucidate the potential protective effect that the concomitant infection with intestinal parasites, especially helminths, could provide to patients with RA. In the period from May to July 2015, a literature review was carried out through Pubmed (1970–2015) and Scopus databases (English and Portuguese idioms), with the use of the following keywords: 'rheumatoid arthritis,' 'helminths,' 'immunopathogeny' and 'hygiene hypothesis'.

Immunopathogenesis of rheumatoid arthritis

The synovium or synovial membrane is considered as that tissue where the inflammatory process begins and perpetuates in RA, with the occurrence of a predominantly mononuclear inflammatory infiltrate, synovial hyperplasia and vascular proliferation associated with the production of proinflammatory cytokines. This hyperplastic synovium constitutes the synovial pannus that, through the invasion of the subchondral bone and underlying cartilage and also of tendons and ligaments, leads to joint destruction.[3,8] The basic mechanism proposed is the loss of immunological tolerance to self-antigens in a genetically susceptible individual, triggering synovitis.[3] In relation to mechanisms of the innate immune response, neutrophils, macrophages, mast cells and natural killer cells participate in this inflammatory response in the synovium.[3] Macrophages participate both in the role of antigen-presenting cells, as effector cells, through the release of the so-called pro-inflammatory cytokines (e.g. tumor necrosis factor (TNF)-α and IL-1β, IL-6, IL-12, IL-15, IL-18 and IL-23), reactive oxygen species, and production of prostanoids and extracellular matrix metalloproteinases.[3] It is assumed that TNF-α plays a central role in the pathogenesis of RA, promoting the release of other inflammatory mediators (i.e., cytokines with autocrine and paracrine action) and that the activation of lymphocytes and macrophages contribute to exacerbate the synovitis, besides promoting a direct activation of osteoclasts, which induce bone resorption.[3]

Classically, RA is described as an autoimmune disease mediated by T cells, especially effector Th1 and Th17 cells.[5,8]

The differentiation of monocytes into osteoclasts is indirectly promoted by TNF through the activation of the receptor activator of nuclear factor kappa-B ligand (RANKL), a member of the superfamily of TNF.[9] This action of TNF turns out to implicate this factor in the inflammatory bone resorption in cases of RA, since the result of RANKL activation stimulates the differentiation and activation of osteoclasts, besides inhibiting the apoptosis of these cells.[10] Furthermore, IL-17 production by Th17 lymphocytes, present in high levels in the synovia of patients with RA, regulates the expression of RANKL, contributing to osteoclastogenesis and progression of joint damage.[9] Although the frequency of regulatory T cells $CD4^+$ and $CD25^+$, responsible for inhibiting the proliferation and production of cytokines by effector T cells, is increased in the synovial fluid of RA patients, it is unclear whether these cells are activated in this environment, taking into account that there is a loss of self-tolerance to self-antigens, which contributes to the persistence of the joint inflammatory process.[9] Moreover, T cell apoptosis is inhibited, probably due to the high level of anti-apoptotic cytokines such as IL-2, IL-4, and IL-15, present earlier in RA.[9]

There is also a contribution of humoral immune response in RA, through the differentiation and proliferation of B cells that produce cytokines and can function as class II antigen presenting cells, contributing to the perpetuation of synovitis.[9] The presence of autoantibodies against the Fc portion of IgG molecules, such as the rheumatoid factor, which illustrates the humoral component in RA, is detectable in 70–80% of patients, but such molecules can also be found in healthy individuals and in patients with other systemic diseases.[9] Antibodies against the citrullination of arginine to citrulline as a result of deamination (anti-cyclic citrullinated peptides) may be present in up to 70% of patients, and these molecules appear early in patients with RA.[9] The exact role of these autoantibodies in the pathogenesis of RA has still not been cleared up, but it is known that seropositive patients in high titers to these antigens tend to exhibit a more aggressive disease, with greater joint damage and bone erosion, as well as with extra-articular manifestations.[3,5]

Immunopathogenesis of intestinal parasites infection

Parasites such as helminths may modulate the immune response, inducing an anti-inflammatory environment that favors their survival within the host, that is, these parasites suppress proinflammatory immune responses in order to maintain their life cycle.[3,11] Intestinal parasitic infections are chronic phenomena, and re-infestation is often seen; and such organisms, in addition to the inhibitory changes that they cause in innate and adaptive immune responses, also have mechanisms to escape the host immune response by reducing their immunogenicity.[5] In general, helminths survive within the host and cause persistent infections, apparently because of a decrease in the innate immune response against the parasites.[5,12] The combined action of mast cells and eosinophils contributes to the containment of intestinal parasites.[5] Such parasites are resistant to phagocytosis and to cytocidal mechanisms of macrophages and neutrophils.[5] Moreover, some helminths may also activate the alternative pathway of the complement system and are resistant to the lysis mediated by proteins pertaining to that system.[5]

In helminth infections, the parasites induce the production of IL-10 and of Th2 cytokines (IL-4, IL-5, IL-9, and IL-13), modifying the stimulation of macrophages to an alternative activated phenotype, which favors the anti-inflammatory response of Th2 cells and the eosinophilic response.[3,12] Helminths also inhibit IFN-α, IL-1β and IL-17, suppressing the inflammatory immune response of Th1 and Th17 cells.[3,12,13] The helminths secrete excretory-secretory products, such as ES-62, which are glycosylated and act by inducing Th2 cytokines and the expansion of regulatory T cells.[13] Moreover, the amount of regulatory T cells ($CD4^+$ $CD25^+$ $FOXP3^+$) that produce IL-10 and TGF-β increases after infection by helminths,[3,11] thus contributing to the permanence of the parasite inside the host.

The homeostasis generated by these immune responses prevents an overreaction against parasites, a thing which also would impair the host, ensuring the survival of helminths.[11,13]

Protective effect of helminth infections in rheumatoid arthritis

In 1970, Greenwood noted that individuals living in Nigerian villages, despite the high incidence of positive cases for rheumatoid factor, had rheumatic disease of a benign course, with a good prognosis and no radiological signs of severity.[14] Given the high prevalence of parasitic infectious diseases in that population, it was suggested that the host response to multiple parasites would somehow interfere in the course of autoimmune diseases.[14] The delay in the establishment of diagnosis, the difficulties of access to medical expertise, the low compliance to treatment and failure or delay in the prescription of disease-modifying drugs negatively impact the prevalence and severity of autoimmune diseases.[15] Thus, patients from developing countries should present more significant morbidity and mortality.[15] However, RA is less common in certain areas of tropical countries, where a high incidence of infectious diseases, especially parasitic ones, is observed.[16] In northeastern Brazil, less severe autoimmune rheumatic disease was also observed, partly due to possibly endemic parasitic infestations.[17] In 1989, Strachan proposed his "hygiene hypothesis" theory: the reduction of exposure to common pathogens, such as helminths, increased the prevalence of allergic and autoimmune diseases in areas where sanitary conditions improved.[3,6,12,13,18–21]

Intestinal parasites are suppressors of proinflammatory immune response, so these organisms can live in equilibrium with the host immune system.[3,12] Thus, in addition to causing disease, they also act as potent modulators of the immune system.[3] The parasites related to protective effects of the aggressiveness of the disease in patients with RA, already described in the literature, are *Schistosoma mansoni*, *Schistosoma japonicum*, *Ascaris suum*, *Heligmosomoides polygyrus bakeri* and *Hymenolepsis diminuta*.[3,12,20,21] Such pathogens inhibit the secretion of Th1/Th17 cytokines, induce the appearance of tolerant dendritic cells and promote the proliferation of regulatory T cells.[21] The infection by *Schistosoma mansoni* or

by *S. japonicum* can modify the function of dendritic cells, macrophages, NK cells and B cells, leading to an expansion of Th2 cells and of regulatory T cells responsible for maintaining self-tolerance.[11,18] The infection of mice with *Schistosoma japonicum* prior to the induction of arthritis by collagen (interval of 2 weeks) significantly attenuated the clinical signs of arthritis, with decreases in synovial hyperplasia, infiltration of synovial mononuclear cells, angiogenesis in inflamed synovia, osteoclast activation, and joint destruction.[11] A lower production of IFN-γ and an increase in IL-4 and IL-10 were observed, together with decreases in proinflammatory cytokine (TNF-α, IL-1 β, IL-6 and IL-17, IFN-γ, RANKL) levels; these findings suggest a predominance of Th2 response and a reduction of Th1 response.[11,18] This change in the immunological profile explains the lower aggressiveness and even the absence of joint disease in the studied models.[11,18] However, the infection of mice with *Schistosoma japonicum* after the collagen-induced arthritis could not reverse the immune response already installed, nor the subsequent joint damage.[11]

Studies using *Ascaris suum* extract (a non-pathogenic product to humans) administered both orally and parenterally in a murine model of arthritis induced by zymosan and collagen demonstrated anti-inflammatory effects of the extract, in order to reduce hyperalgesia and the damage to the articular cartilage.[15,17] The mechanism associated with the response to this helminth extract was a diminished release of inflammatory mediators – nitric oxide, IL-10, and IL-1β – to the mice's joints.[17] There was no change in TNF-α levels.[17]

In an individual with an autoimmune rheumatic disease such as RA, the helminth infection has the potential to alleviate the symptoms and improve the progressive course of the disease, thanks to the induction of an immune response by Th2 cells, antagonistic to the response by Th1 cells present in autoimmune disease.[6,19] In addition to inhibiting Th1 cytokines, the induction of regulatory cytokines (IL-10 and TGF-β), the production of regulatory T cells FOXP3 and the activity of alternatively activated macrophages also would influence in the protective effect of helminth infections in patients with RA.[20]

Given the hypothesis that individuals infected with helminths would be less susceptible to other inflammatory diseases, the parasitic infection could influence the treatment of diseases mediated by Th1 cells.[20]

The helminth infections and the products derived from helminths (such as ES-62) are valuable tools to the understanding of the immune responses caused by these parasites, possibly helping in identifying new clinically relevant therapeutic targets.[13] Immunomodulatory products – purified or synthesized – obtained from helminths must be studied, in order to be used clinically.[15,19] The challenge is to identify and characterize specific antigens of a given helminth that target the protective response, and also antigens/molecules that would serve as indicators in the development of new biopharmaceutical agents for treating a number of diseases, among them RA.[20]

Conclusion

RA is a debilitating and painful systemic illness, whose immunopathogenesis involves innate and adaptive immune mechanisms, especially with Th1 cell activity and release of inflammatory cytokines, for example, TNF-α. An early treatment can modify the aggressive and disabling course of this disease. Today, we can rely on effective biological therapies for the treatment of RA, targeted to blocking specific inflammatory cytokines. It is assumed that the generation of an immunologically balanced environment, as a result of the infection by helminths, could reduce the severity of a concurrent autoimmune rheumatic disease. A better understanding of the modulation pathways of the anti-inflammatory action provided by the infection with helminths, or by their secretory products, may lead to new therapeutic strategies (capable of inhibiting more broadly the inflammatory cytokines) and amplify the therapeutic arsenal currently available for RA.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Mota LMH, Cruz BA, Brenol CV, Pereira IA, Rezende-Fronza LS, Bertolo MB, et al. Consenso 2012 da Sociedade Brasileira de Reumatologia para o tratamento da artrite reumatoide. Rev Bras Reumatol. 2012;52:135–74.
2. Azevedo ABC, Ferraz MB, Ciconelli RM. Indirect costs of rheumatoid arthritis in Brazil. Int Soc Pharm Outcomes Res. 2008;11:869–77.
3. Anaya JM, Shoeenfeld Y, Rojas-Villarraga A, Levy RA, Cervera R. Autoimmunity – from bench to bedside. 1st ed. Bogotá: El Rosario University Press; 2013.
4. Braz AS, Andrade CAF, Mota LMH, Lima CMBL. Recomendações da Sociedade Brasileira de Reumatologia sobre diagnóstico e tratamento das parasitoses intestinais em pacientes com doenças reumáticas autoimunes. Rev Bras Reumatol. 2015, http://dx.doi.org/10.1016/j.rbr.2014.10.010.
5. Abbas AK, Lichtman AH, Pillai S. Cellular and molecular immunology. 7th ed. Philadelphia: Elsevier; 2012.
6. Bezerra ELM, Vilar MJP, Barbosa OFC, Santos SQ, Castro MA, Trindade MC, et al. Lúpus eritematoso sistêmico (LES): perfil clínico-laboratorial dos pacientes do Hospital Universitário Onofre Lopes (UFRN-Natal/Brasil) e índice de dano nos pacientes com diagnóstico recente. Rev Bras Reumatol. 2005;45:339–42.
7. Alcântara AC, Leite CA, Leite AC, Sidrim JJ, Silva FS Jr, Rocha FA. A longterm prospective real-life experience with leflunomide in juvenile idiopathic arthritis. J Rheumatol. 2014;41:338–44.
8. Ortiz-Flores AM, Ledesma-Soto Y, Calleja EA, Rodríguez-Sosa M, Juárez I, Terrazas LI. *Taenia crassiceps* infection does not influence the development of experimental rheumatoid arthritis. BioMed Res Int. 2012:316980.
9. Andersson AK, Li C, Brennan FM. Recent developments in the immunobiology of rheumatoid arthritis. Arthritis Res Ther. 2008;10, article 204.
10. Schett G, Hayer S, Zwerina J, Redlich K, Smolen JS. Mechanisms of disease: the link between RANKL and arthritic bone disease. Nat Clin Pract Rheumatol. 2005;1:47–54.
11. Song X, Shen J, Wen H, Zhong Z, Luo Q, Chu D, et al. Impact of *Schistosoma japonicum* infection on collagen-induced arthritis in DBA/1 mice: a murine model of human rheumatoid arthritis. PLoS ONE. 2011;6, article e23453.

12. McSorley HJ, Maizels MR. Helminth infections and host immune regulation. Clin Microbiol Rev. 2012;25:585–608.
13. Pineda MA, Al-Riyami L, Harnett W, Harnett MM. Lessons from helminth infections: ES-62 highlights new interventional approaches in rheumatoid arthritis. Clin Exp Immunol. 2013;177:13–23.
14. Greenwood BM, Herrick EM, Voller A. Can parasitic infection suppress autoimune disease. Proc R Soc Med. 1970;63: 19–20.
15. Rocha FAC, Leite AKRM, Pompeu MML, Cunha TM Jr, Verri WA, Soares FM, et al. Protective effect of an extract from *Ascaris suum* in experimental arthritis models. Infect Immun. 2008;76:2736–45.
16. Mattsson L, Larsson P, Erlandsson-Harris H, Klareskog L, Harris RA. Parasite-mediated down regulation of collagen-induced arthritis (CIA) in DA rats. Clin Exp Immunol. 2000;122:477–83.
17. Rocha FAC. Protective role of helminthiasis in the development of autoimune diseases. Clin Dev Immunol. 2006;13:159–62.
18. He Y, Li J, Zhuang W, Yin L, Chen C, Li J, et al. The inhibitory effect against collagen-induced arthritis by *Schistosoma japonicum* infection is infection stage-dependent. BioMed Central Immunol. 2010;11.
19. Osada Y, Kanazawa T. Parasitic helminths: new weapons against immunological disorders. J Biomed Biotechnol. 2009;2010:743758.
20. Matisz CE, McDougall JJ, Sharkey KA, McKay DM. Helminth parasites and the modulation of joint inflammation. J Parasitol Res. 2011;2011:942616.
21. Versini M, Jeandel PY, Bashi T, Bizzaro G, Blank M, Shoenfeld Y. Unraveling the hygiene hypothesis of helminthes and autoimmunity: origins, pathophysiology, and clinical applications. BioMed Cent Med. 2015;13.