

Autoantibodies in leprosy and leishmania patients – more evidence on the association of infections and autoimmunity

The association of infectious diseases with autoimmunity, either presenting with clinical manifestations, or only detected by the emergence of autoantibodies, has been widely documented.¹ Viral, bacterial, and parasite infections may be involved in the arousal, flare, and even be involved in the prevention of autoimmune disease.^{1,2} This issue of the RBR features two studies on the prevalence of autoantibodies in patients with infectious diseases. Ribeiro *et al.* evaluated the frequency of rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), anticardiolipin (aCL) antibodies, and anti- β 2 glycoprotein I (anti- β 2GPI) antibodies in patients with leprosy. Among the 158 patients evaluated, 76 patients had articular manifestations, while 82 patients had no articular involvement. The control group consisted of 129 healthy adults, matched for age and sex, and residing in the same geographical area as the patients. The majority of the patients in both groups, (with and without articular involvement), had the generalized leprosy presentation (VV). The authors found a low, and not significantly different frequency of RF, anti-CCP, ANA, and ANCA in leprosy patients, (in both groups), and in normal controls. But the prevalence of aCL and anti- β 2GPI antibodies was significantly elevated in the leprosy patients as compared to the controls, although there was no significant association with articular involvement. IgM was the predominant isotype for both antibodies. Almost half of the leprosy patients (48.7%) had at least one antiphospholipid antibody. In addition, the authors found an association between aCL positivity and clinical manifestation, as patients harboring aCL antibodies more frequently had the generalized VV type of disease ($p = 0.002$). There was no association between the presence of aCL or anti- β 2GPI antibodies and reaction episodes, but among the patients with reactions, those who were aCL-positive, had

ENL (100% of cases), while among aCL-negative patients, 57% had ENL. Although a high concordance rate was found for the presence of aCL and anti- β 2GPI antibodies, no thromboembolic manifestations were recorded.

In the second study, Harimoto *et al.* evaluated 90 patients affected with *Leishmania*, (45 patients had visceral leishmaniasis and 45 patients had cutaneous leishmaniasis), for the presence of anti-*Leishmania* antibodies, as well as for RF, ANA, anti-DNA, anti-Sm, anti-RNP, anti-Ro, anti-La, aCL antibodies, and complement levels (C3 and C4). As expected, 100% of the patients with visceral leishmaniasis had anti-*Leishmania* antibodies, as compared to 62.3% among patients with limited cutaneous disease. Significant elevated titers of ANA (albeit in some only borderline values), but not anti-DNA, were detected only among 4.4% of patients with visceral disease, as well as elevated titers of aCL antibodies (IgG isotype), as compared to patients with cutaneous leishmaniasis. Decreased complement levels was also evident only in patients with visceral disease (13.3% of patients had significantly decreased levels of C3).

In both studies the authors compare and discuss their results in light of the growing literature on the presence of autoantibodies in both diseases. Some of their results are consistent with previous studies while others differ. Overall the variable reported prevalence of autoantibodies in the two current studies, as well as in previous reports in the literature, might stem from methodological differences, such as the type of assay used, the definition of cut off points, heat inactivation of the sera, patient selection, and ethnic and geographical variations in the patients groups. But one of the consistent results in both studies is the elevated frequency of antiphospholipid antibodies. aCL and anti- β 2GPI antibodies were significantly more frequent in leprosy patients than in controls, while ANA and aCL antibodies were more frequently detected in patients with visceral leishmaniasis. The increased

frequency of ANA and aCL antibodies in patients with visceral leishmaniasis is compatible with previous reports and studies,³⁻⁵ illustrating the similarities both in clinical and laboratory features between visceral leishmaniasis and systemic lupus erythematosus (SLE). In addition, cross-reactivity of ANA and anti-*Leishmania* antibodies has been reported.⁶

Several groups have documented elevated levels of antiphospholipid antibodies (aCL, anti- β 2GPI, anti-prothrombin) in several infectious diseases such as syphilis, viral diseases (including hepatitis C, Parvo B19 and HIV infection), malaria and leprosy, without the clinical features of the antiphospholipid syndrome (APS).⁷ The elevated titers are often transient and decline and disappear after the resolution of the infection.⁷⁻⁹ But in a minority of patients the association of infections with antiphospholipid antibodies can lead to severe, often fatal thrombotic complications, namely to "catastrophic APS".⁷

The results of Ribeiro *et al.* of an increased frequency of anti- β 2GPI antibodies among leprosy patients, together with data from our group and others,⁹⁻¹² which also documented increased levels of anti- β 2GPI antibodies in these patients, question the previous notion that aCL antibodies associated with infections are β 2GPI-independent, as opposed to aCL β 2GPI-dependent antibodies in autoimmune disease. Altogether these results support the view that in the setting of infection, aCL antibodies are heterogeneous in their dependence on β 2GPI,⁹⁻¹² and that infections may trigger the induction of "pathogenic" antiphospholipid antibodies in predisposed subjects.⁹

The production of autoantibodies in leprosy and leishmaniasis may be explained by several mechanisms. In the more generalized form of both diseases (VV in leprosy and visceral leishmaniasis), there is a decrease up to absence of cellular immunity, and a predominance of T-helper 2 cytokines, which can skew the immune system towards a robust humoral response. In both disease states (VV in leprosy and visceral leishmaniasis) patients present with diffuse hypergammaglobulinemia, similar to other infections such as with *Schistosoma mansoni*, *T. cruzi* and *Plasmodium*. The induction of autoantibodies can be attributed to the polyclonal activation and proliferation of B cells, some with autoreactivity, belonging to the library of natural antibodies in healthy subjects.¹³ In the setting of *Leishmania* infection, soluble parasite-derived antigens from *L. major* and *L.*

donovani have been found to be mitogenic and to trigger the production of immunoglobulins with autoreactivity.¹³ Mixed cryoglobulinemia induced by HCV is another example of persistent polyclonal activation leading to a mixture of polyclonal and monoclonal autoantibodies, which ultimately cause autoimmune disease.¹⁴

Molecular mimicry or structural homologies between infectious and host components may underlie the mechanism of autoantibodies production, as in the case of rheumatic fever, where the M component of the streptococcus membrane shares homologies with heart, brain, and joint synovium peptides. The association of Guillain-Barre syndrome with *Camphylobacter jejuni* infection provides another example of molecular mimicry underlying the autoimmune manifestation. Cross-reactive antigens between infectious agents and self-antigens have been demonstrated for *M. Leprae*,¹⁵ and *M. Tuberculosis*,¹⁶ and the inhibition of anti-Sm, anti-RNP, and anti-SSB by intact *Leishmania* promastigotes, supports a homology between nuclear antigens and *Leishmania*.¹³

Epitope spreading or the emergence of a new antibody or T-cell response to a new epitope (subdominant or cryptic) on the same or on another antigen has been demonstrated in experimental models and human disease. In SLE authors have demonstrated intermolecular spreading from Sm antigen to RNP reactivity,¹⁷ and in rheumatic fever, the chronic autoimmune state affecting the heart valves, can result in an immune response against collagen or laminin.^{1,2} Infections can play an important role on the induction of autoimmunity also through the release of sequestered antigens after tissue damage, or by upregulation of the display of cryptic epitopes, under the inflammatory milieu, thus introducing new antigens to the immune system.

In summary, the two new studies published in this issue of the RBR add to our growing understanding on the intricate relationship between infections and autoimmunity, and specifically, concerning antiphospholipid antibodies, in susceptible subjects, infections may trigger the induction of pathogenic antiphospholipid antibodies.

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