Infection and rheumatic diseases: cause, consequence or both?

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ACTA REUMATOL PORT. 2014:39;113-115

This editorial's title could be in a nineteenth century medical journal, but can still be published nowadays. In fact the disease that was described in 1859 by Sir Alfred Barring Garrod as Rheumatoid Arthritis (RA) for the first time, was considered first by Billings, in 1912, as an immune response to chronic infection, and later on by Cecil, in 1929, as a consequence of streptococcal infection, since the serum of 94% of RA patients agglutinated with suspension of these microorganisms[1-2]. RA is an immune mediated disease in which autoantibodies and autoreactive T cells in peripheral blood and synovial fluid promote synovial inflammation, proliferation and ultimately joint destruction as well as systemic manifestations, through progressively better known mechanisms regarding inflammation and osteoimmunology. However, the initial trigger that leads to the cascade of events leading to the disease known as RA is still unknown and mechanisms related with the exposure to several viral and bacterial antigens are still being studied in the XXI century. Viral infections that lead to arthritis, such as Parvovirus B19, infections by latent virus of the herpesvirus family, such as Epstein Barr virus (EBV), and bacterial infections that might cause periodontitis, such as Porphyromonas gingivalis, have all been implicated in etiopathogenesis of systemic immune mediated diseases, particularly RA[3,4].

Besides, it is currently well known that several microorganisms can cause reactive arthritis weeks after causing infection, mostly in HLA-B27 positive individuals[5]. Patients with chronic infections (hepatitis C, HIV) may develop musculoskeletal manifestations, or even full-blown rheumatic diseases that need to be thoroughly addressed. Notably, after the advent of highly active anti retroviral therapy, HIV positive patients, mostly those that are immunocompetent have increasingly immune mediated manifestations (arthritis, vasculitis and sicca syndrome) and decreasing infectious complications[6]. On the other hand, rheumatic patients who are immunosuppressed have increased risks of several infectious diseases. Clinical trials and meta-analyses of clinical trials are usually not sufficient to evaluate the risks of several infectious hazards. This was uncovered with the risk of mycobacterial infections (even atypical agents) in patients exposed to TNF inhibitors (TNFi), the risk of hepatitis B reactivation in patients exposed to rituximab in endemic areas and the risk of multifocal leukoencephalopathy due to JC virus reactivation not only in patients immunosuppressed with chemotherapy protocols including rituximab, but also in rheumatic patients[7-9].

Several of the before mentioned aspects are addressed in this edition of Acta Reumatologica Portuguesa (ARP). Telles JP *et al.* evaluated the rheumatic manifestations of 69 acquired immunodeficiency syndrome (AIDS) patients. The authors found that arthralgia was the main manifestation affecting 39.1% of the patients, although arthritis was less frequent, but still relevant (8.6%). The authors also found that antinuclear antibody (ANA) positive patients were older and had higher viral counts. In this paper it is posed the hypothesis that antigenic similarities between HIV-gp120 and nuclear antigen may explain this later finding. A correlation between ANA or rheumatoid factor positivity and rheumatic manifestations was not found[10].

Lube GE *et al.* presented a case series of 4 condyloma acuminatum related with Human Papilloma Virus infection (HPV) in 289 childhood systemic lupus patients (cSLE) that have been followed during a period of 29 years. Three out of 4 patients were sexually active, and all were immunosuppressed (with cyclophosphamide and/or azathioprine) and treated with, at least,

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moderate dose corticosteroids. All were infected with oncogenic serotypes, and presented preneoplastic lesions. This evidence raises the necessity of systematic gynaecologic follow up of these patients, as well as HPV vaccination prior to sexual activity[11].

A case of reactive arthritis related with Salmonella goldcoast infection is also published. It's the case of a 28 year old male, HLA B27 positive, who presented severe asymmetric polyarthritis, sacroiliitis, fever and severe bloody diarrhoea. The patient underwent a flexible rectossigmoidoscopy, which revealed focalized and irregular areas with hyperaemia and superficial erosions, suggesting inflammatory bowel disease. However the pathological exam was nonspecific. Stool culture was positive for Salmonella goldcoast in 3 samples. The patient had the odd habit of drinking aquarium water, which could explain this persistent unusual infection. After treatment with ciprofloxacin and nonsteroidal anti-inflammatory drugs (NSAIDs) the patient improved. The environmental exposure and stool culture were the keys to the diagnosis[12].

Mycobacteria usually cause disease in immunosuppressed hosts, and, in fact, in the United States most of the mycobacterial infections in biologic treated patients are due to nontuberculous mycobacteria (NTM). Most of these forms in immunosuppressed hosts are systemic. However, these agents may also cause disease in immunocompetent hosts, which tends to be more localized, and usually related with penetrating injury. Yano K *et al*. present a case of a 68 year old woman, previously healthy, that presented with chronic monoarthritis of the wrist, misdiagnosed as RA. The diagnosis of *Mycobacterium intracellulare* arthritis and osteomyelitis was made after synovial and ulnar epiphysis surgical biopsy. Histopathological examination showed granulomas with caseous necrosis and Ziehl-Neelsen staining revealed acid-fast bacilli. Polymerase chain reaction was positive for *Mycobacterium intracellulare* one week after surgery and the cultures were positive after nine weeks. The authors notify the good results of anti-tuberculous drugs for immunocompetent patients also treated surgically. Immunosuppressed patients seem to have a clearly worse prognosis. Synovial biopsy for histological and microbiological analysis is essential in the diagnosis of chronic monoarthritis[13].

The risk of tuberculosis (TB) among TNFi users is thoroughly evaluated, and it was substantially diminished after the introduction of rigorous guidelines regarding the treatment of latent tuberculosis (LTB) before starting those therapies. Many guidelines advocate, besides clinical evaluation of risk factors for TB and physical examination, the use of chest radiography and purified protein derivative (PPD) or interferon-γ release assay (IGRA) testing before starting TNFi in order to exclude active TB or LTB. However, most of these guidelines do not define the correct procedure regarding the risk of new TB infection in patients chronically exposed to TNFi, although some advocate annual LTB screening, particularly in patients who live, travel or work in environments where TB exposure is likely[14]. Paula DF publishes a letter presenting a study on which 47 RA patients exposed to TNFi and 58 RA patients on conventional DMARDs were retested for PPD during their follow up. Patients previously exposed to chemoprophylaxis or with prior TB were excluded. Three out 47 patients exposed to TNFi and 6 out of 58 on conventional DMARDs had a conversion of the PPD test at the median time of follow-up of 36 months (defined as an increase ≥ 6 mm when compared with baseline PPD). Besides finding no differences between both groups regarding PPD conversion, there were no TB reports. It is clear that this study was not powered to detect differences in TB incidence, but raises a question whether PPD conversion can predict the risk of TB in patients exposed to TNFi. The answer can only be given if this studied is replicated in a larger population and with a longer follow-up[15].

In short, the rheumatologist of the XXI century has to be aware of rheumatologic manifestations of viral diseases, uncommon agents that may cause infectious arthritis or reactive arthritis and still has to manage the potential infectious complications related with immunosuppression in general and with the last decade advent of targeted therapies that lead to new, and sometimes unpredictable, infectious risks.

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