Infections and rheumatic diseases

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Submitted: December 2022
Accepted: March 2023
Published: May 2023

ABSTRACT

Infections and rheumatic diseases have shared a close relationship since time immemorial. Some rheumatic diseases are a direct consequence of infections while others have been associated with certain microbes without an established causal link. The above relationship is becoming more and more complex due to rapid advances in therapeutics, and also because of factors such as climate change and worldwide travel. This is a brief review of the major facets of this relationship and demonstrates that clinicians not only have to keep up with all the advances in management of rheumatic diseases but also must remain vigilant about both common as well as opportunistic and unfamiliar infections and their consequences.

INTRODUCTION

Rheumatic diseases are a group of conditions that have an inflammatory basis and are often autoimmune in nature. These could affect the musculoskeletal system as well as other organs, such as lungs, kidneys and skin. Infections and rheumatic diseases have always had an intriguing relationship and that continues to evolve with increasing complexity.[1] Infections could not only cause systemic immune-mediated diseases but also be the most dreaded complication associated with the use of immunosuppressives for treating rheumatic conditions.[2]

INFECTIONS CAUSING RHEUMATIC DISEASES

Several rheumatic diseases develop in response to pathogenic infections. Mechanisms such as molecular mimicry are thought to play a role. Molecular mimicry results from antigenic similarity between molecules found on infectious agents and host tissues.[3] A wide variety of microbes can also cause intra-articular (septic arthritis) or intra-osseous (osteomyelitis) infections but these conditions are not traditionally considered rheumatic in nature. The following are examples of rheumatic diseases caused by infections:

Viral arthritis – Many viruses have been implicated in viral arthritis including parvovirus B19, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), human T cell leukaemia virus (HTLV)-1 and arboviruses. The arboviruses or arthropod-borne viruses are mostly transmitted by mosquitoes and belong to two main groups: alphaviruses (e.g., chikungunya virus) and flaviviruses (e.g., dengue virus). Acute arthralgia and arthritis are well recognised complications of viral infections and 1% of all cases of acute polyarticular arthritis have a viral cause.[4] It is usually self-limiting but highlights the importance of taking a comprehensive travel history.

Reactive arthritis – This is a form of inflammatory arthritis that develops a few weeks after either a sexually acquired (e.g., *Chlamydia trachomatis*) or gut associated (e.g., Campylobacter, Salmonella, Shigella and Yersinia) infection.[5] Reactive arthritis usually resolves spontaneously but if the symptoms persist for more than six months then disease modifying agents such as methotrexate or sulfasalazine should be considered.

Lyme disease - This is caused by *Borrelia burgdorferi* and is transmitted to humans through an infected tick bite. It may start as a red and circular rash around the

Citation: Mukherjee, Infections and Rheumatic Diseases, South Sudan Medical Journal, 2023;16(2):60-63 DOI: https://dx.doi.org/10.4314/ssmj.v16i2.5

site of a bite (erythema migrans – seen in about 70 to 80%) which slowly expands with partial central clearing. The other typical symptoms include fever, headache and fatigue with myalgia and arthralgia. Most patients are treated effectively with antibiotics over a few weeks. In some cases, particularly if left untreated, patients may develop inflammatory arthritis as well as neurological and cardiac problems.[5] The term 'chronic Lyme disease' remains poorly defined and has been controversial. 'Post-treatment Lyme disease syndrome' refers to a number of nonspecific symptoms including fatigue, widespread musculoskeletal pain and cognitive problems that are seen in 5 to 15 per cent of the patients despite antibiotic therapy and, in most cases, these gradually resolve over six to twelve months.

Rheumatic fever – Acute rheumatic fever (ARF) occurs following Group A streptococcal throat infection although emerging evidence suggests this could also be a consequence of streptococcal skin infection. It can affect different organs and joint disease is thought to be the second most common manifestation. Unless ARF is effectively treated, it could lead to chronic rheumatic valvular heart disease.[5]

INFECTIONS CONSIDERED AS POTENTIAL TRIGGER FOR RHEUMATIC DISEASES

Although the exact mechanisms involved in the pathogenesis of classical rheumatic diseases remain mostly unknown, both genetic and environmental factors are thought to play a vital role. An important component of the latter are infections and several mechanisms, other than molecular mimicry, have been proposed. These include epigenetic modifications induced by microorganisms, epitope spreading and pathogen persistence.[3,6,7] The following are examples of rheumatic diseases where infective agents have been implicated as potential triggers:

Rheumatoid arthritis (RA) – This mainly causes pain, swelling and stiffness affecting peripheral joints. Various microorganisms have been associated with the development and persistence of RA. Investigators have reported several immunological, molecular and microbiological findings which suggest *Proteus mirabilis* could play a role in the pathogenesis.[5] Moreover, periodontitis is a well-known risk factor for RA and *Porphyromonas gingivalis*, a gram-negative anaerobe, that commonly causes periodontitis, has also been strongly associated.[6]

Systemic sclerosis (SSc) – This is an uncommon autoimmune disorder that causes hardening of the skin and also affects other internal organs. Molecular mimicry has been thought to play a role during the early phases of SSc and, although several organisms have been implicated, the strongest evidence seems to be in favour of human cytomegalovirus (hCMV) and Epstein Barr virus (EBV).[6]

Axial spondyloarthropathy – This is a rare form of inflammatory arthritis that mainly affects the spine and sacroiliac joints and results in spinal pain and stiffness. Several immunological and microbiological studies have identified evidence that appears to link *Klebsiella pneumoniae* to its development.[5]

Systemic lupus erythematosus (SLE) – This is also a rare autoimmune disease that causes inflammation in skin, joints and other organs. Human endogenous retrovirus (HERV) infection can genetically predispose individuals to SLE while EBV infection is thought to be a trigger for its development.[1]

Sjögren's syndrome (SS) – This is a rare autoimmune disease that presents as dryness of eyes and mouth but may also affect joints, nerves and several other organs. HCV, EBV and HTLV1 have been put forward as potential causative agents in SS.[6]

Vasculitis – These are a group of uncommon autoimmune diseases that cause inflammation of blood vessels and are classified depending upon the size of vessel affected. Nasal carriage of *Staphylococcus aureus* has been linked to granulomatosis with polyangiitis (GPA, previously called Wegener's granulomatosis), a small-to-medium vessel vasculitis. Chronic HCV infection has been implicated in mixed cryoglobulinaemic vasculitis while Henoch-Schönlein purpura has been associated with Group A streptococci and parvovirus B19. Polyarteritis nodosa has also been linked to HBV infection.[6]

INFECTIONS RELATED TO TREATMENT OF RHEUMATIC DISEASES

The last three decades have witnessed a revolution in antirheumatic disease management because of the availability of increasing therapeutic options. These include various biological agents that reduce inflammation by targeting specific cytokines like tumour necrosis factor (TNF), depleting particular subsets of cells, for example B lymphocytes, or blocking T cell co-stimulation. More recently, several small molecules have been introduced and these work by inhibiting intracellular signalling (e.g., Janus Kinase (JAK)-signal transducer and activator of transcription (STAT) pathway).[2] However, all these agents are also associated with adverse effects, particularly the increased risk of infection, both by common and opportunistic pathogens. The following are some examples of the latter:

Mycobacterial infections - Biological agents such as TNF inhibitors are associated with risk of reactivation of latent tuberculosis (TB) infection and that is higher with monoclonal antibodies against TNF (e.g., infliximab) compared to the soluble TNF receptor blocker etanercept.[8] Various national and international organisations have produced guidelines about screening and treatment of latent TB

before initiating biological therapy. There are a limited number of studies looking at the risk of TB reactivation with non-anti-TNF biologics and although the results are reassuring, the British Society for Rheumatology guidance recommends following the same advice as that for anti-TNF agents until more data becomes available. Moreover, non-tuberculous mycobacteria appear to be a greater concern in countries which have a low prevalence of TB.[8]

Herpes Zoster – This results from reactivation of latent *Varicella zoster* virus (VZV) due to reduction in immunity because of aging or immunosuppression and is also known as shingles. Biological agents such as TNF blockers and small molecules like JAK inhibitors have been associated with an increased risk of shingles[8] and vaccination of high-risk population could potentially help to reduce that. The non-live vaccine Shingrix provides very good protection against shingles and postherpetic neuralgia and is an alternative to the live vaccine Zostavax which is contraindicated in immunocompromised patients. The recently published European Alliance of Associations for Rheumatology (EULAR) guidelines recommend that patients who are thought to be non-immune to VZV should be made aware about post-exposure prophylaxis if they come into contact with someone having chickenpox or shingles.[9]

Pneumocystosis – *Pneumocystis jirovecii* pneumonia (PJP) is a fungal opportunistic infection in immunocompromised hosts and has also been seen in autoimmune rheumatic disease patients receiving immunosuppressive therapy.[8] According to EULAR guidelines, PJP prophylaxis appears to be of benefit in patients treated with prednisolone higher than 15–30 mg (or equivalent) daily for more than 2–4 weeks. Concomitant use of other strong immunosuppressants potentially increase that risk but there is a relative lack of data relating to these individual agents.[9]

Progressive multifocal leukoencephalopathy (PML) – This is a rare demyelinating central nervous system infection caused by reactivation of John Cunningham virus and is frequently fatal. It has been reported in rheumatic diseases treated with strong immunosuppressives but the risk seems to higher for SLE patients receiving rituximab.[2]

Reactivation of HBV – The EULAR guidance recommends HBV screening for all rheumatic disease patients being considered for immunosuppressive agents. However, the risk seems to be particularly high for patients with chronic HBV infection and for those treated with rituximab and a hepatology opinion has been recommended in such cases for consideration of prophylactic treatment.[9]

Mucocutaneous candidiasis – Interleukin 17 inhibitors have been associated with an increased risk of mucocutaneous candidiasis. These patients should be closely monitored for that and antifungal prophylaxis might be needed in some circumstances.[10]

Finally, it is important to consider local epidemiology because endemic fungi in USA and Leishmania in Mediterranean countries can cause severe opportunistic infections in patients with rheumatic diseases receiving immunosuppressive treatment.[7]

SPECIAL CONSIDERATIONS

Global warming and climate change – Higher temperatures and increased rainfall facilitate spread of several infections that have rheumatic manifestations, such as vector-borne diseases like dengue and enteric diseases like salmonella.[11] The tick vectors of *Borrelia burgdorferi* have now spread to greater parts of Europe while local transmission of chikungunya has been reported in France and Italy.[12]

International travel and migration – Consequent to huge increases in movement of people between tropical and temperate countries, clinicians can now come across unfamiliar infections. For example, many western countries are now considered to be free of leprosy, a chronic infection caused by *Mycobacterium leprae*, and the diagnosis could be missed unless suspected. This usually presents with skin and neurological involvement but musculoskeletal features are the third most common. These include Charcot's arthropathy, acute as well as chronic symmetrical polyarthritis and tenosynovitis although other rheumatic manifestations such as enthesitis, sacroiliitis and cryoglobulinaemic vasculitis have also been occasionally reported.[13]

Hygiene hypothesis – This postulates that exposure to some infective agents during childhood could provide protection against development of allergic and autoimmune rheumatic diseases in the future. This is based on epidemiological and clinical data which show an increase in prevalence of these conditions in western countries in conjunction with reduced rates of infections. Consequently, there could potentially be an increase in autoimmune rheumatic diseases in some developing countries as they adopt healthier standards of living including access to clean water.

COVID-19 pandemic – The full extent of the relationship between rheumatic diseases and COVID-19 infection remains unclear. An important lesson from the recent pandemic is that rheumatic diseases on their own are associated with only a modest additional risk and the principal factors that determine a poor outcome are active disease, comorbidities including increased age, and use of medications like rituximab and glucocorticoids.[14] It is now clear that hydroxychloroquine is entirely ineffective against COVID-19 infection although anti IL-6 agents like tocilizumab have been shown to improve outcomes in

some patients with severe or critical disease.

Vaccinations - Patients with rheumatic diseases have an increased risk of infections and vaccinations can play a vital role in prevention. However, the immunological response to vaccines can be reduced in those receiving strong immunosuppressive therapy and various strategies including appropriate timing of vaccination have been used to improve efficacy. Moreover, certain vaccines, such as the ones against SARS-COV-2, have been implicated in the development of *de novo* rheumatological conditions as well as disease flares in those with existing illnesses.[15]

CONCLUSION

Infections and rheumatic diseases share a fascinating relationship. Some rheumatic diseases are the consequence of specific infections while others have been associated with several microbial agents although the definitive proof of a causal link in such cases mostly remain elusive. The ever-evolving field of advanced therapeutic options has made it possible to effectively treat a wide range of rheumatological diseases that were previously considered refractory but these agents are also frequently linked to a significant increase in the incidence of common infections as well as to the emergence of potentially life-threatening opportunistic infections. Moreover, external factors such as global warming and migration of people have led to spread of diseases to new geographical locations and clinicians must be vigilant about such unfamiliar infections and their consequences.

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