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Infectious mimics of rheumatoid arthritis

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A B S T R A C T

Rheumatoid arthritis (RA) can have various infectious mimics. As immunosuppressive agents used in treatment can aggravate the underlying infections, correct diagnosis of RA and ruling out infections is important. Numerous viral infections (Parvovirus B19, Hepatitis B, Hepatitis C, Chikungunya and other alphaviruses, human immunodeficiency virus (HIV) and various other viruses), mycobacterial infections (Poncet's disease, tubercular septic arthritis, and leprosy), bacterial arthritis, brucellosis and Lyme disease are among common infections that mimic RA. Widespread travel and tourism, especially to exotic areas, high risk sexual behavior and widespread use of immunosuppressive and chemotherapeutic agents has led to numerous outbreaks of infections in areas where these infections were never reported before. Hence, rheumatologists all over the world should be familiar with musculoskeletal manifestations of infections. History of travel, comorbid fever, skin rash, genital ulcers, urethral discharge, the consumption of unpasteurized milk, lymphadenopathy, tenosynovitis, low platelet count, and positive Mantoux test can offer potential diagnostic clues. Serological testing, cultures, specific radiological signs and deoxyribonucleic Acid (DNA) amplification techniques often aid in diagnosis. Treatment mainly consists of antimicrobial agents, analgesics, and nonsteroidal anti-inflammatory drugs (NSAIDs). However, immunosuppressive agents including steroids and disease modifying anti-rheumatic drugs (DMARDs) are needed occasionally in different refractory and prolonged illnesses. Most of the times, episodes of arthritis are self-limiting and respond to treatment of underlying cause.

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However, few infections like Chikungunya and Lyme's disease can lead to chronic arthritis as well.

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Introduction

Rheumatoid arthritis (RA), one of the most common inflammatory arthritis, affects about 0.5%–1% of general population [1]. Early diagnosis and initiation of therapy with disease modifying anti-rheumatic drugs (DMARDs) and treat to target (T2T) are key strategies for achieving best outcomes including remission. However, there is considerable variation among patients in regard to both number and types of joints involved, especially at the onset of RA. Moreover, early stage RA closely mimics various other forms of inflammatory arthritis including infections [2]. Risk of overdiagnosis in patients with early arthritis that would have resolved without DMARDs, has been estimated at ~8%, according to the 2010 EULAR/ACR criteria for RA [3].

Numerous bacterial, mycobacterial, and viral infections often present with musculoskeletal manifestations including in arthralgia and arthritis (Table 1). Since the treatment of RA primarily comprises immunosuppressive agents, this can be detrimental if the underlying cause is an infection. Furthermore, most incidences of viral infection-related arthritis are self-limiting illnesses; therefore, they do not need long-term DMARDs therapy. Hence, differentiating infections from RA is of prime importance [4]. In underdeveloped and developing countries where the prevalence of infections remains high, both rheumatologists and general practitioners must be familiar with infections that mimic RA and other forms of inflammatory arthritis. In the era of widespread and frequent travelling including to exotic places, even developed countries are witnessing frequent outbreaks of infectious diseases that were never reported before [5]. This issue becomes even more relevant in the era of pandemics like COVID-19. The various clinical clues which help in making this diagnosis are given in Table 2 (see Table 2).

Viral infections

Viral infections are responsible for ~1% of acute arthritis worldwide. Parvovirus B19, hepatitis and various alpha viruses are among the most common causative agents of viral arthritis [4,6]. Newer viruses

Table 1

Infections mimicking rheumatoid arthritis.

Viral infections:

1. Parvovirus B19
2. Hepatitis B
3. Hepatitis C
4. HIV
5. HTLV-1
6. Chikungunya and other alphaviruses
7. Other viral infections such as coxsackie virus, Epstein-Barr virus, measles, mumps and rubella virus

Mycobacterial infections

1. Poncet's disease
2. Tubercular septic arthritis
3. *Mycobacterium leprae* (Lepra reactions and chronic arthritis of leprosy)

Bacterial arthritis

1. Polyarticular septic arthritis

Others

1. Brucellosis
 2. Lyme arthritis
 3. Reactive arthritis
-

Table 2

Clinical clues to infectious arthritis.

| |
|---|
| History |
| <ul style="list-style-type: none"> • Asymmetrical arthritis at presentation • Predominantly large joint involvement • Arthralgia rather than arthritis • Fever and constitutional symptoms • Rash and other skin lesions like erythema nodosum • Travel history to endemic and exotic places • IV drug abuse • High risk sexual activities • Contact with animals and consumption of unpasteurized milk and dairy products |
| Examination |
| <ul style="list-style-type: none"> • Lymphadenopathy • Characteristic rash • Hepatomegaly/Splenomegaly • Predominant tenosynovitis • Features of disseminated infection |
| Laboratory investigations |
| <ul style="list-style-type: none"> • Thrombocytopenia and/or pancytopenia • Low titre ANA positivity • Reactive Mantoux Test • Radiology suggestive of tuberculosis and other infections • Serological tests indicative of infections • Positive cultures and nucleic acid amplification techniques |

are constantly being added to this list as increased travel has contributed to outbreaks of various vector-borne and arbovirus-related infections worldwide. On the other hand, the prevalence of some viral infections like hepatitis B, mumps, and rubella has decreased due to increased vaccination coverage; hence these infections are presently less commonly recognized as etiology of viral arthritis [4].

Viral infections must always be considered as causative agents for acute onset arthritis, especially if involvement is polyarticular at the onset, associated with fever and other viral infections-related prodromal symptoms and in patients with significant travel history to endemic regions in the recent past. Besides history and clinical examination, viral serology plays a key role in diagnosis of viral arthritis. Clinicians must remain aware that both rheumatoid factor (RF) and antinuclear antibody (ANA) can be positive in viral infections, though in low titer. Viral infection related arthritis is often self-limiting and necessitates symptomatic treatment only; therefore, underlying viral infection may need appropriate antivirals [4–6].

Parvovirus B19 infection

Parvovirus B19 infection is widely prevalent and most of adults (60%–90%) are seropositive for IgG anti-B19 antibody [7]. Although most of the cases in pediatric population remain asymptomatic, classical presentation of febrile illness with “slapped cheek” also occurs commonly. Parvovirus infection also causes transient aplastic anemia and bone marrow suppression in adults [4].

Rheumatic manifestations including arthralgia and arthritis are seen in ~10% of the children and >50% of symptomatic adults [4,8]. In children, articular involvement is mainly oligoarticular, primarily affecting large joints. In contrast, articular involvement in adults is typically additive and symmetrical and involves small joints like wrist and interphalangeal joints that closely mimic RA. However, frank synovitis and joint effusion are rarely present. These joint manifestations most commonly occur in acute phase and coincide with appearance of IgM antibodies.

Parvovirus arthritis is also characterized by rise in inflammatory markers like C-reactive protein (CRP) and presence of autoantibodies like rheumatoid factor (RF), anti-nuclear antibody (ANA), anti-extractable nuclear antigen (anti-ENA), antiphospholipid antibodies that appear transiently [4,9].

Parvoviral arthritis is self-limiting but can occasionally last up to several months, and it can be managed with non-steroidal anti-inflammatory drugs (NSAIDs) alone [4]. Rarely, arthritis can be very severe and may require other agents like intravenous immunoglobulins [10]. Because parvovirus arthritis does not require treatment with immunosuppressive agents, high index of suspicion must be there in immunologically vulnerable population and must be confirmed through appropriate serological testing. Routine testing is not recommended in early arthritis as parvovirus infection accounts for <0.5% cases of early arthritis [11].

1. Hepatitis B virus infection

Hepatitis B, a DNA virus that is transmitted vertically, sexually, or parenterally, affects ~400 million people worldwide [4]. Patients experience joint pain symptoms during both prodromal phase of acute infection and chronic infection. Symmetrical arthritis involving hand, knee, and wrist joints resembling RA occurs in prodromal phase of acute infection and can be the only presenting feature of the same. Arthritis may last from days to months and often subsides with onset of jaundice [12]. RF is positive in ~25% of these patients whereas ~40% of patients show low complement levels [8]. The presence of fever, rash, malaise, myalgia, transaminitis (highly elevated Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) may suggest hepatitis B related arthritis. Positive serology (HBsAg, IgM anti-HBc) provides a definitive diagnosis in appropriate clinical setting. Only symptomatic treatment is needed as symptoms usually subside in 2–3 weeks.

Nearly one fourth of patients with chronic HBV infection experience joint symptoms, although frank synovitis is rare. However, these symptoms should alert a treating rheumatologist for underlying polyarthritis nodosa (PAN) and cryoglobulinemia [4].

More and more cases of HBV reactivation are being reported in patients with underlying RA and other rheumatological disorders, especially in those taking biological agents including rituximab. This can sometimes prove fatal too [13].

2. Hepatitis C virus infection

Estimably, ~3% of world's population is chronically infected with hepatitis C virus (HCV) [4]. Nearly half of patients with acute HCV infection and ~5% patients with chronic HCV infection develop arthritis that can directly be attributed to HCV infection. While the majority of these patients develop polyarticular arthritis involving small joints of hands and feet that closely mimic RA, some also present as lower limb predominant oligoarticular arthritis involving large joints. However, the disease tends to be milder and is usually self-limiting [14,15]. As ~80% of these patients are RF positive, it is extremely difficult to differentiate them from RA [13]. HCV-related arthritis is most commonly treated with analgesics and NSAIDs. Rarely, low dose corticosteroids and DMARDs have been used in severe cases and non-responders [4,13].

Presence of arthralgia and arthritis in the setting of purpura, polyneuropathy, and renal involvement in HCV-positive patients is due to cryoglobulinemic vasculitis (CryoVas) syndrome. The latter is usually treated with a combination of antivirals and immunosuppressive agents like corticosteroids, cyclophosphamide, and rituximab [4]. Interferon alpha which was used as treatment of HCV infection could lead to polyarticular arthritis that mimics RA [16]. Coexistent autoimmune disorders like RA, Systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) in chronic HCV patients pose both diagnostic and therapeutic challenge. Presence of specific antibodies like Anti-cyclic citrullinated peptide (CCP), anti-double-stranded DNA (anti-dsDNA), anti-SSA (anti-Ro), and anti-SSB (anti-La) autoantibodies and erosive changes on radiographs often facilitate diagnosis [13].

3. HIV virus

Nearly 10% of patients of untreated HIV infection develop mono or polyarthritis that can mimic RA as well. After widespread availability of combination antiretroviral therapy (cART), there was a marked decline in HIV-related arthritis. However, an immune reconstitution syndrome occurring after the

initiation of cART may unmask the underlying autoimmune disease like RA or SLE. Co-existing HBV/HCV infection, reactive arthritis, and arthritis related to syphilis or gonorrhea also result in joint symptoms in individuals with HIV infection [4].

4. HTLV-1

Human T-cell lymphotropic virus type 1 (HTLV-1) infection is endemic in Japan and the Caribbeans. Inflammatory arthritis has been reported in patients with HTLV-1 infection with or without adult T-cell leukemia/lymphoma. Both polyarthritis resembling RA and oligoarthritis affecting mainly shoulder, wrist and knee have been documented in few studies [17,18]. Radiographs may reveal erosive changes as well. Both RF and ANA can be positive in HTLV-1 infection related arthropathy. However, characteristic skin lesions, fever, and myalgia that occur at the onset of joint symptoms in persons living in endemic regions or those with history of travel to these regions raises the possibility of HTLV-associated arthropathy [18]. This is usually treated with NSAIDs and low dose corticosteroids. However, severe cases have been treated with DMARDs and even with anti-TNF agents as well [19].

5. Chikungunya and other old-world alphaviruses

Alphaviruses are one of the major genera among arboviruses (transmitted by mosquitoes) that cause arthritis. Old-world alphaviruses like Chikungunya, Ross river virus, Sindbis-group virus, O'nyong-nyong virus and Mayaro virus (MAYV) cause syndrome of fever and arthralgia [4].

Chikungunya virus (CHIKV), a major arboviral infection of tropical areas, is transmitted by female *Aedes* mosquito. Frequent travel and growing tourism have made CHIKV as one of the major public health concerns of recent times as its outbreaks have occurred worldwide, affecting ~6.5 million people between 2004 and 2011 [20]. CHIKV infection has been subdivided into acute (<3 months) and chronic (>3 months) phases. Acute phase is characterized by high grade fever, conjunctivitis, skin rash, myalgia, and severe polyarthritis. Arthritis is symmetrical disease and involves both small and large joints, and thus, it mimics RA. This is also accompanied by very painful bursitis and tenosynovitis. Patients with underlying co-morbidities tend to have more severe joint manifestations. Fever usually lasts for 5–10 days. As per various epidemiological studies, 4%–78% of patients with CHIKV arthritis advance to chronic phase. In chronic phase, patients have polyarthritis which mimics RA and peripheral spondyloarthritis [21]. Various studies have documented that nearly one fourth of all patients remain symptomatic even after 20 months of infection [21,22].

CHIKV arthritis must be strongly considered in patients either in endemic areas or in travelers who recently visited affected areas and now presented with high-grade fever and debilitating joint pains. Patients may have transient anemia, leucopenia, and thrombocytopenia. Other etiologies of acute febrile illness like malaria, dengue, enteric fever, and Zika virus infection must be considered. Various methods of definitive diagnosis include RT-PCR (0–7 days of infection), IgM CHIKV (Day 7 till 2–3 months) and IgG CHIKV (Day 7 onwards and in chronic phase as well). In chronic phase, RF, anti-CCP and HLAB-27 may be used to rule out RA and spondyloarthritis [21].

In acute phase, most patients need adequate hydration and analgesics like paracetamol only. After ruling out dengue virus infection, NSAIDs may be given in severe cases once platelet count recovers. Oral steroids in low doses have been used if symptoms last >3 weeks and there is confirmed synovitis or tenosynovitis. Codeine and tramadol have also been used in combination with other regimes. Pregabalin and amitriptyline may also be added in the case of neuropathic symptoms [21]. Although many studies have shown inconsistent results in acute phase, both the WHO and Brazilian guidelines recommend hydroxychloroquine (HCQ) for persistent or resistant joint pain [21,23].

DMARDs have shown benefit in chronic CHIKV arthritis. In an observational study from India, 49% of the enrolled patients benefited from a combination of methotrexate and HCQ [24]. Further, the guidelines recommend the usage of DMARDs like methotrexate, sulfasalazine, and leflunomide and biologic agents like anti-TNF agents in treatment resistant cases. Seropositive patients are more likely to benefit from DMARDs therapy [21].

6. Other viruses

Various other viruses like coxsackie viruses, Epstein-Barr virus, measles virus, mumps and rubella may rarely cause acute self-limiting arthritis that mimics RA [4].

Mycobacterial infections

Tuberculosis (TB) continues to be a global public health problem. In 2019, ~10 million people fell ill with this disease and 1.4 million lost their lives due to TB. In recent times, the prevalence extrapulmonary TB is on rise [25]. People living with HIV/AIDS (PLHA), elderly, those with systemic diseases and those receiving immunosuppressive illnesses are more likely to have extrapulmonary tuberculosis [26]. Musculoskeletal tuberculosis accounts for 1%–3% cases of tuberculosis and 10%–11% of extrapulmonary tuberculosis [27]. Spinal tuberculosis, osteomyelitis, tubercular arthritis, and Poncet's disease (Reactive arthritis due to tuberculosis elsewhere) are major forms of musculoskeletal tuberculosis. Among these diseases, Poncet's disease and tubercular arthritis may closely resemble RA.

1. Poncet's disease

It is a form of reactive arthritis that occurs in the presence of extra-articular tuberculosis. Although tuberculosis is very common, Poncet's disease is relatively less commonly reported, even from countries where tuberculosis is endemic. Lack of awareness among general practitioners and rheumatologists and the absence of standard diagnostic criteria may contribute to underreporting of this unique entity [28]. In literature, joint involvement has been described as polyarticular, non-erosive, and non-deforming, though recently in case series with large sample size, oligoarticular presentation is more common (40.7%–56.5%). Even in these studies, a significant number of patients (27.6%–43.5%) had polyarticular involvement and thus closely mimicked RA [28,29]. In a case series from India, > 90% of patients had no prior diagnosis of tuberculosis and nearly half of them had no constitutional symptoms as well. Mantoux positivity (see Fig. 1). is reported to be up to 80% but is not universal. [28]. As RF and anti-CCP antibody can be positive in 62% and 37%, respectively, of patients of tuberculosis, the differentiating Poncet's disease from RA can be very difficult at times [30]. A diagnostic criteria (Sharma and Pinto's criteria) has been proposed [28].



Fig. 1. Positive Mantoux test in a patient with Poncet's arthritis.

Hence, all patients with new onset arthritis, especially in endemic areas must be enquired about fever and other constitutional symptoms, cough, expectoration, hemoptysis, skin rash, change in bowel habits, and history of contact with any active case. A thorough examination including lymph nodes and skin for erythema nodosum must be performed. Before initiating immunosuppressive therapy for RA and other inflammatory arthritis, chest X-ray to rule out pulmonary TB must be made mandatory. Adding immunosuppressive agents in this setting is detrimental because it can lead to dissemination of tuberculosis. Treatment of Poncet's disease is antitubercular therapy (ATT) and symptomatic treatment with NSAIDs. Almost all cases show complete resolution of symptoms after completion of ATT [28]. A case of Poncet's disease from South Africa was successfully treated by ATT and NSAIDs, but subsequently developed RA after few years [30]. Therefore, need of keeping such patients on follow-up and observing them for development of inflammatory arthritis in future cannot be undermined. This is especially important for seropositive patients of Poncet's disease as seropositivity can represent pre-clinical phase of RA as well.

2. Tubercular septic arthritis

Tubercular arthritis is classically described as chronic monoarthritis involving large joints such as hip and knee. Nearly 85% of tubercular arthritis involves a single joint [27]. Although oligo- or polyarticular involvement is uncommon, when present closely it resembles RA and inflammatory arthritis, poses a diagnostic challenge. However, in endemic countries like India, polyarticular tubercular arthritis is not unheard of [27]. It must be remembered that a significant proportion of patients suffering from TB are RF and anti-CCP antibody positive [30]. As previously damaged joints are more prone for developing TB, tubercular arthritis has also been reported in patients with RA and other inflammatory arthritis and connective tissue disorders like SLE as well [31].

Hence, tubercular arthritis must be considered in new-onset oligo-polyarthritis, especially in countries with high burden of tuberculosis, in elderly and pediatric population, and immunocompromised individuals. As substance abuse has increased alarmingly in recent past, rheumatologists will see more and more cases of polyarticular arthritis in future as intravenous drug use has been regarded as important risk factor for the same [32]. Patients may have associated fever and other constitutional symptoms, skin lesions like panniculitis (erythema nodosum) and features of tubercular infection elsewhere in body. On evaluation, diagnostic clues may include a positive Mantoux test (50%–90% cases) and a characteristic radiological sign known as “Phemister's triad of juxta-articular osteopenia, peripheral erosions and joint space narrowing” [30]. Synovial fluid smear and culture for acid fast bacilli (AFB) and synovial biopsy must be considered with a low threshold in case of patients at risk, as inappropriate use of immunosuppressive agents may be detrimental. Treatment is 6 or 9 months of ATT and symptomatic treatment with NSAIDs. Surgical treatments are reserved for severe cases like abscess and concomitant osteomyelitis [30,31].

Leprosy

Leprosy is a granulomatous disease caused by *Mycobacterium leprae* and predominantly occurs in tropical countries. However increased travel and tourism and widespread use of immunosuppressive agents, particularly anti-TNF agents, have led to outbreaks of leprosy even in Western world. Although it has primarily been regarded as illness of skin and peripheral nerves, ~75% of patients have musculoskeletal involvement which includes acute onset polyarthritis of lepra reactions and chronic symmetrical polyarthritis, both of which closely resemble RA. More importantly, joint involvement may be the only presenting feature of leprosy, thus making accurate diagnosis even more difficult [33].

1. Arthritis in lepra reactions

It is characterized by acute onset polyarthritis that affects joints of hands and feet in symmetrical manner, thereby closely mimicking RA. Sometimes large joints like shoulder, elbow, knee and ankle may also get affected. Other features of lepra reactions like fever, worsening of skin lesions and

paresthesia are often present along with joint symptoms [33]. In a study from India, 63% of patients presented with erythema nodosum lesions along with joint symptoms related to lepra reactions [34]. Various studies have suggested that arthritis may be present in 50%–65% of patients of lepra reactions and usually subsides within 4 weeks in most of the times [33–36]. Arthritis may rarely have chronic or relapsing remitting course [33]. Treatment consists of multidrug therapy (MDT) and corticosteroids. Prednisolone at 1 mg/kg/day is usually started and tapered gradually every 2–4 weeks. In severe cases, thalidomide, clofazimine and anti-TNF agents may be required [33,37].

2. Chronic symmetrical arthritis in leprosy

Chronic symmetrical polyarthritis involving hands and feet may be present in leprosy without any concomitant reactional states and may last for years (Mean duration of 11 years in various studies) and may be present even if leprosy is currently inactive. Joint symptoms respond very well to multidrug therapy (MDT) but the response is never complete. This may lead to deformities like ulnar drift, swan neck and boutonniere deformities, thus closely resembling RA. Sacroillitis, enthesitis, tenosynovitis and cryoglobulinemic vasculitis have been reported in various studies [33–35].

Diagnosis of arthritis associated with leprosy is very difficult even in the presence of skin manifestations and often overlooked even in the endemic regions. RF and ANA positivity in significant proportion of leprosy patient further makes diagnosis challenging. However, it must be considered and dedicatedly searched for, in cases of unexplained arthritis. Presence of skin lesions, tenosynovitis, and thickened nerves are the diagnostic clues [33,34]. Anti-CCP antibody is nearly always absent in leprosy, thus may add to the diagnosis [33]. Definitive diagnosis is the demonstration M. leprae bacilli in synovium. However, these are either not conspicuous or not present in synovium. Other findings on synovial biopsy include non-specific granuloma and epithelioid cells. Exclusion of other causes of symmetrical polyarthritis and circumstantial evidence of leprosy is key to diagnosis and often serves the purpose [33].

Bacterial arthritis

Although classically regarded as acute onset monoarthritis, ~15%–20% of cases have oligoarticular or polyarticular presentation and thus resemble RA [38]. Majority of the patients either have some underlying illnesses like immunocompromised state, prosthetic joint, malignancy, diabetes mellitus, chronic kidney disease, and RA or are IV drug abusers [39]. However, septic arthritis is not very common in PLHA population [40]. Occasionally, polyarticular septic arthritis has been reported in immunocompetent individuals as well [38,41]. While most of the patients are febrile, high spiking fever with chills is usually rare. Elderly patients are usually afebrile [41,42]. Mortality in polyarticular septic arthritis is ~50%, which is nearly 5 times higher than that of myocardial infarction [41].

Septic arthritis should be suspected in susceptible patients who present with acute onset arthritis and fever. Evidence of concomitant skin, respiratory or urinary tract not only gives diagnostic clue but also provides an idea about likely causative pathogen. High ESR and CRP and raised total leucocyte count (TLC) usually doesn't differentiate septic arthritis from other forms of inflammatory arthritis [42]. Serum procalcitonin may help in diagnosis as it is often raised in bacterial infection and is not even affected by intake of glucocorticoids and NSAIDs. In a meta-analysis, a cutoff value of 0.5 and 0.3 ng/mL were able to respectively "rule-in" and "rule-out" bacterial arthritis with a sensitivity and specificity of about 90% [43]. Demonstration of causative organism in synovial fluid, either by Gram stain or bacterial culture provides definitive diagnosis. Prompt aspiration of purulent material, IV antibiotics (2–6 weeks), and early rehabilitation of joints are key aspects of treatment of septic arthritis.

Septic arthritis in patients with RA poses a diagnostic challenge as it is difficult to differentiate septic arthritis from disease activity [44]. As per British Biologics Registry, as compared to td-DMARDs, the use of anti-TNF agents doubles the risk of septic arthritis [45]. Risk with other biologic agents like rituximab and abatacept is less pronounced [46]. As RA activity is usually not associated with fever, presence of fever and other risk factors may be clues to septic arthritis in patients with RA. Whenever suspected, diagnosis should be promptly confirmed by arthrocentesis and examination of fluid. Septic arthritis in RA is associated with high morbidity and mortality [44].

Disseminated gonococcal infection often presents with fever, polyarthralgia/arthritis and skin lesions. Tenosynovitis often accompanies bacteremic phase. Skin lesions include macules, papules and pustules and are often painless and non-pruritic. Vesicles, bullae and erythema nodosum lesions are other skin manifestations [47]. Although this bacteremic phase may mimic RA, characteristic skin lesions and history of high-risk behavior usually gives clue. Diagnosis is confirmed by Gram staining, culture, or nucleic acid amplification techniques. Genital, rectal, and pharyngeal smears have better yield than synovial fluid [48].

Brucellosis

Spread by consumption of unpasteurized milk and dairy products and direct contact with infected animal, brucellosis is one of the commonest zoonotic disease worldwide. It is rarely fatal and has acute and chronic phases of illness [49]. Whereas acute phase presents mostly as flulike illness, chronic phase is characterized by fever, fatigue, malodourous perspiration, depression, uveitis, lymphadenopathy, splenomegaly and various osteoarticular manifestations [50].

Osteoarticular features have been reported in 11–85% of patients of brucellosis in different published series. It can cause both septic and reactive arthritis. This variation is due to different study populations and differences in causative agents and diagnostic criteria [50]. In a meta-analysis, arthralgia and arthritis were present in 65% and 26% patients, respectively. Sacroiliitis and spondylitis are fairly common and are present in 12–36% patients [51]. In an Indian study, nearly half of patients had sacroiliitis and 17% of patients had polyarthritis [52]. In another study, 38.8% of patients had mono/pauciarthritis [53]. Hence, it can easily be misdiagnosed as RA.

Diagnosis of brucella arthritis can be challenging and often requires a high index of suspicion. Careful history taking and consideration of other features that favor brucellosis are important potential diagnostic clues. Specific antibody tests, blood, and synovial fluid cultures often aid in diagnosis. Additionally, 50–80% have positive blood cultures. Combinations of doxycycline with either rifampicin or streptomycin give excellent results. Peripheral arthritis is usually nondestructive [50].

Lyme arthritis

Lyme disease is caused by spirochaete *Borrelia burgdorferi*, which is a tick-borne infection. This is endemic in certain parts of North America, Europe, and Asia [54]. While in acute phase, characteristic skin lesions (erythema migrans), flulike symptoms, CNS and cardiac manifestations predominate, joint symptoms mainly occur in late phase of illness (mean duration, 6 months after skin lesions). However, in many of the cases, early phases of Lyme disease remain asymptomatic and thus presents with arthritis for the first time [55]. Most of the times one or few large joints are involved intermittently (mostly knee). Small joints, temporomandibular joints and periarticular structures like bursae and tendons may be affected, particularly in earlier episodes [55,56]. Hence, the presentation of this disease may be oligoarticular or even polyarticular at times and thus mimics RA.

However, in contrast to RA and other inflammatory arthritis like reactive arthritis (most close differential diagnosis of Lyme arthritis), joints in Lyme arthritis are swollen and warm, but are not very painful. Minimal pain occurs only during passive movements of joint despite prominent signs of inflammation [55]. History of travel to endemic area, especially in late spring and early summers, and characteristic skin lesions (If present or noticed) may help. RF and Anti-CCP antibody testing are usually negative in Lyme arthritis but ANA can be positive in low titer. Arthrocentesis is useful in distinguishing it from septic arthritis. Diagnosis is usually done by serological testing, which is done as per CDC guidelines which recommends a two-step approach. All samples are tested initially by enzyme linked immunosorbent assay (ELISA) and if the result is either positive or equivocal, the same is confirmed by Western blotting [55,57].

Most of the cases respond to antibiotics like doxycycline, amoxicillin, ceftriaxone, and penicillin G. Symptomatic treatment with NSAIDs is often required [55]. However, few cases persist and even worsen after antibiotic therapy and thus described as “post-infectious Lyme arthritis” [54]. This post-infectious arthritis requires treatment with DMARDs like methotrexate and hydroxychloroquine. In severe and refractory cases, anti-TNF agents like etanercept and adalimumab have been used. However,

in contrast to chronic inflammatory arthritis like RA, this usually resolves from 4 months to 4 years and thus doesn't require long term treatment with DMARDs [55]. Histopathology of synovium closely resembles RA [54].

Reactive arthritis

It has been described as non-septic inflammatory arthritis that occurs after genitourinary or gastrointestinal infection [58]. Arthritis occurs due to dysregulated immune response against micro-organisms and infection is resolved in most cases by the time patient presents with joint symptoms. Typical presentation is acute onset oligoarthritis affecting large joints of lower limbs. However, the involvement of small joints with polyarticular involvement is also seen in 15–20% patients [59]. No evidence of infection is found in nearly 20–30% patients despite dedicated history, physical examination, and investigations including cultures, serologies, and chlamydial antigen detection in urine or urogenital swab by polymerase chain reaction (PCR). Hence, the diagnosis of such patients can easily be confused with RA [60].

However, involvement of sacroiliac joints (30%) periarticular structures like enthesitis (30%) and dactylitis (17%), eye manifestations like conjunctivitis (30%) and uveitis (5%), genitourinary involvement in the form of cervicitis and salpingo-oophoritis in females and circinate balanitis and prostaticitis in males may help in differentiating reactive arthritis from RA and other forms of chronic arthritis [59,61,62]. Reactive arthritis also has characteristic skin manifestations (up to 50%) like keratoderma blennorrhagica, erythema nodosum and mucosal ulcers that often aid in diagnosis [62]. HLA-B27 is positive in 30–50% cases and predicts the involvement of sacroiliac joint, more severe arthritis and extra-articular features. Reactive arthritis is usually self-limiting illness that lasts usually for 3–5 months but can progress to chronic arthritis in 20–25% cases [63].

Joint symptoms are mostly managed with NSAIDs and intra-articular steroids. Systemic steroids are mostly needed in severe polyarthritis and extra-articular manifestations. Sulfasalazine has been used in both acute and chronic reactive arthritis especially when NSAIDs are ineffective. Other DMARDs like methotrexate, leflunomide and azathioprine are useful in peripheral arthritis [64,65]. Refractory cases have successfully been treated with biologics like anti-TNF agents [66]. Antibiotics are only indicated if there is evidence of active infection [67].

Summary

Increasing outbreaks of rare and newer infections, and concept of early initiation of immunosuppressive agents in RA have made infection-related arthritis more relevant than before. Numerous bacterial, mycobacterial and viral infections have predominant musculoskeletal manifestations that closely resemble RA, especially in early stages. As most incidences of infection-related arthritis are self-limiting, they do not require to be treated with steroids and DMARDs. Immunosuppressive agents may aggravate underlying infections as well. Hence, both rheumatologists and general practitioners across the globe must be familiar with rheumatological manifestations of both common and emerging infections.

Practice points

- RA closely mimics various bacterial, mycobacterial, and viral infections, especially in early stages.
- Comorbid fever and rash, lymphadenopathy, asymmetric and large joint involvement at the onset, prominent tenosynovitis, low platelet count, and presence of radiological signs are early clues to underlying infections.
- Thorough evaluation must include history of recent travel, IV drug abuse, contact with persons including high risk sexual activities and extra-articular features of suspected infections.
- Serological testing, cultures, and DNA amplification techniques are often helpful.
- DMARDs and steroids should only be initiated once infections are reasonably ruled out.

Research agenda

- Role of infections in pathogenesis of RA needs to be investigated. Since infection related arthritis has positive RF and ACPA and sometimes have either chronic or relapsing-remitting course, these may contribute to the evolution of RA.
- Investigations including serological tests and DNA amplification techniques that accurately diagnose infectious arthritis and are cost effective and readily available, must be available in near future.

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Declaration of competing interest

None declared.

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