Review

Virally associated arthritis 2008: clinical, epidemiologic, and pathophysiologic considerations

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Abstract

Several viruses have been associated with the development of inflammatory arthritis, including the hepatitis viruses (hepatitis B virus and hepatitis C virus), HIV, the parvovirus B19, the human T-cell lymphotropic virus-I, and the alphaviruses. Here, we review the epidemiology, the pathophysiological mechanisms, the pertinent clinical and laboratory findings as well as the principles of therapy of the most common virus-associated arthritides. We believe that the knowledge of these key diagnostic and therapeutic features of virus-associated arthritides is important for the rheumatologist of the 21st century.

Introduction

The spectrum of human viral infections is vast. Considering their ubiquity, clinically significant rheumatic manifestations, including arthritis, are relatively rare. Despite this generality, viral infections can and do cause a number of clinically important arthritic syndromes. Some are acute, mimicking early-onset rheumatoid arthritis (RA) such as seen in parvovirus B19 and hepatitis B virus (HBV) infection and others. Alternatively, some viral infections are associated with more chronic forms of arthritis, which can be challenging both diagnostically as well as therapeutically. Other infections are important from a public health perspective and the rheumatologist may have the opportunity to make an early diagnosis of a serious or epidemic condition. It is beyond the scope of this review to describe all viral infections with reported arthritic complications. The goal is to highlight those infections that are most relevant to the rheumatology practitioner by providing pertinent information on the pathogen, its epidemiology, presumed pathogenic mechanisms, most common clinical features of articular disease, and principles of therapy.

Classification of viral infections and the pathogenesis of virally associated arthritis

Viral infections can be classified based on a number of microbiologic and molecular features and are organized most broadly as to whether their genomes contain DNA or RNA and whether they encode and replicate through reverse transcriptase. The International Committee on Taxonomy of Viruses has recognized 5,450 viruses as specific species based on molecular structure and organized into families [1]. A more practical approach of classification is to consider the pathogen based on its clinical pattern of infection [2]. Acute viral infections are those with a finite beginning and end in which it appears that the host is capable of overcoming the assault by ridding itself of the invader. Such is the pattern of many common infections, including rhinovirus and influenza, in which there appears to be no significant incidence of viral latency or chronicity. A second and extremely common pattern is that of viral latency. In this model, there may be a clinically apparent or subclinical primary infection followed by a prolonged and often lifelong period of latency with possible periods of clinical or subclinical relapses. Herpes virus infections are classically associated with latency. As examples, varicella zoster virus reactivation is generally associated with a dramatic clinical event (that is, dermatomal zoster) whereas Epstein-Barr virus (EBV) infection is more often associated with recurrent bouts of asymptomatic viral shedding. At the molecular level, latency is even more complex and the intermediate expression of viral components under the influence of both viral and host factors is an area of intense interest and research. Finally, there are relatively few viral pathogens that are associated with chronic replicative persistence. In this

ALT = alanine aminotransferase; ANA = antinuclear antibody; anti-CCP = anti-cyclic citrullinated peptide; anti-TNF = anti-tumor necrosis factor; AST = aspartate aminotransferase; CHIKV = Chikungunya virus; DMARD = disease-modifying antirheumatic drug; EBV = Epstein-Barr virus; HAART = highly active antiretroviral therapy; HBV = hepatitis B virus; HCV = hepatitis C virus; HTLV-I = human T-cell lymphotropic virus type I; IFN-α = interferon-alpha; IVIG = intravenous immunoglobulin; NSAID = nonsteroidal anti-inflammatory drug; PAN = polyarteritis nodosa; PCR = polymerase chain reaction; RA = rheumatoid arthritis; RF = rheumatoid factor; SLE = systemic lupus erythematosus.

model, acute infection may be clinical or subclinical followed by a prolonged and commonly lifelong period of continuous viral replication as seen in all cases of HIV infection, most cases of hepatitis C virus (HCV) infection, and less commonly in adult-acquired HBV infection. Some caution should be exerted in the acceptance of this simplified classification scheme as the concepts of acute, latent, and persistent infections may be oversimplistic. For example, parvovirus B19 represents an infection that – in hosts with normal immune systems – is clinically acute, but the persistence of apparently nonreplicating virus can frequently be demonstrated with molecular techniques in the bone marrow of patients with arthritis and in healthy controls [3]. Despite such limitations of classification by clinical pattern, the approach remains clinically useful.

While our knowledge of the pathogenesis of virally associated arthritis has gaping holes, the disease is believed to develop as the result of several non-mutually exclusive mechanisms, including direct viral infection and the induction or amplification of autoimmunity by the virus. In either case, immune factors are central. When a pathogen invades a joint, it may induce an inflammatory reaction via lytic effects on host tissues, immune complex formation, or the induction of inflammatory cytokines such as the well-documented effects of certain alphaviruses that target mononuclear cells within the joint [4]. Alternatively, viruses can induce autoimmunity and inflammation via numerous mechanisms such as molecular mimicry, bystander activation, or epitope spreading [5]. In most cases of virally associated arthritis, however, the mechanisms are poorly understood.

Hepatitis B virus

Despite widespread vaccination programs, chronic HBV infection remains one of the most common chronic viral infections, with approximately 350 million people infected worldwide [6]. HBV is an enveloped double-stranded DNA virus transmitted parenterally, sexually, or vertically. In the majority of cases during adulthood (>95%), exposure to the virus is followed by a successful host immune response demonstrated by activation of both cellular and humoral immune mechanisms leading to liver inflammation (acute hepatitis) and eventually viral clearance.

Arthritis in patients with HBV can be encountered in two settings: as an RA-like, acute, self-limited polyarthritis during the presymptomatic phase of acute hepatitis B or more rarely as arthritis occurring in the context of HBV-associated polyarteritis nodosa (PAN). In both cases, the pathogenesis of the arthritis is attributed to the deposition of immune complexes containing viral antigens (HBV surface antigen HBsAg or HBeAg) and their respective antibodies (anti-HBs and anti-HBe) in synovial tissues. A direct role for HBV in tissue inflammation has also been proposed, based on the detection of active HBV replication in endothelial cells from diseased tissues in HBV-associated PAN [7]. Whether a similar mechanism is involved in HBV-related arthritis remains to be confirmed.

In a small proportion of patients, during the preicteric phase of acute hepatitis B, a symmetric polyarthritis can develop [8]. The polyarthritis has the typical characteristics of RA with common involvement of the proximal interphalangeal joints, knees, and ankles [8]. Clues to a possible diagnosis of HBV-associated arthritis are the presence of rash (maculopapular, urticarial, or rarely petechial) accompanied by fever, malaise, and myalgias. Rheumatoid factor (RF) can be positive in about one fourth of patients whereas C3 and C4 are found to be low in approximately 40% of patients, indicative of an immune-complex-mediated process. The detection of positive HBsAg, highly elevated aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), and IgM anti-HBc antibodies provides the definite diagnosis of HBV-associated polyarthritis. No treatment is required since the arthritis resolves spontaneously after 2 to 3 weeks.

HBV-associated PAN is decreasing in frequency worldwide [9]. In most cases, PAN develops during the first 6 months of HBV infection and its clinical presentation and course do not differ significantly from those of classical PAN [9]. Arthralgias are common, occurring in approximately 50% of patients, and are usually accompanied by myalgias. Frank arthritis, affecting predominantly large joints (knees, ankles, and wrists), is observed in only a small proportion of patients [9]. The management of HBV-associated PAN includes immunosuppressives (corticosteroids, cyclophosphamide in severe cases) and antiviral therapy (nucleoside or nucleotide analogs). For patients who achieve initial remission, the overall prognosis is good, with less than 10% of patients relapsing [9].

Hepatitis C virus

Chronic HCV infection is a worldwide public health problem, with more than 170 million people affected [10]. HCV is an RNA hepatotropic virus that is transmitted parenterally, mainly through injection drug use. Patients who had been transfused with blood or blood-derived products prior to 1992 and persons with multiple sexual partners are also at increased risk [11]. In contrast to HBV, the majority of adult patients (55% to 85%) exposed to HCV develop chronic infection [10]. Depending on a number of factors such as older age, alcohol abuse, and presence of liver steatosis and coinfections (HIV), around 20% of patients develop end-stage liver disease and 10% develop hepatocellular carcinoma during the course of their chronic infection.

The appearance of articular symptoms in the form of either arthralgias or frank arthritis in a patient with chronic HCV infection often puzzles the caring physician. Joint manifestations in patients with chronic HCV infection can be encountered in four different forms: a coexistent arthropathy (not related to HCV), arthritis in the setting of mixed

cryoglobulinemia, arthritis directly related to HCV (HCV-associated arthritis), and arthritis induced by antiviral therapy (interferon-alpha [IFN-α]) [12]. A correct diagnosis in this setting is not always easy to make and is obviously of paramount importance for the design of the appropriate therapeutic approach.

Probably the most common cause of arthritis in HCV patients is the mere coexistence of another inflammatory (RA, systemic lupus erythematosus [SLE], Sjögren syndrome, and so on) or noninflammatory (fibromyalgia) rheumatic disorder, which can be expected based on the prevalence of these diseases in the particular population. Some of these rheumatic disorders often share clinical manifestations and laboratory findings with chronic HCV infection without articular manifestations such as sialadenitis, generalized fatigue, positive RF (40% to 65%), cytopenias, antinuclear antibodies (ANAs) (10%), or low C4 levels. The presence of certain laboratory (anti-cyclic citrullinated peptide [anti-CCP] for RA, anti-double-stranded DNA for SLE, and anti-Ro/La for Sjögren syndrome) or radiological (erosive changes in RA) findings is helpful for the differential diagnosis.

The treatment of these coexistent rheumatic disorders should always be made after careful evaluation of the status of the underlying chronic liver disease (mild hepatitis, advanced fibrosis, and compensated or decompensated cirrhosis) [13]. In cases in which long-term immunosuppression with medications with potential hepatotoxicity is planned (methotrexate and leflunomide), a baseline liver biopsy and a consultation with a hepatologist are appropriate. In patients with advanced fibrosis in liver biopsy or with clinical evidence of decompensated cirrhosis (ascites, encephalopathy, or coagulopathy), these medications should be avoided [14]. In patients with less advanced disease and stable liver function, these medications can be used with close monitoring of liver function. Recently, there have been a number of small open studies demonstrating the short-term safety of anti-tumor necrosis factor (anti-TNF) and anti-B cell (rituximab) agents in rheumatic patients with chronic HCV infection [13]. For anti-TNF agents (etanercept), especially, data from a small randomized single-center study indicated its safety and efficacy when given in combination with antiviral treatment in patients with chronic hepatitis C [15]. The most recent recommendations for the treatment of RA from the American College of Rheumatology also suggested that anti-TNF agents can be given in patients with chronic compensated HCV infection [14]. Results from ongoing randomized trials are expected to provide more definite data regarding the safety of anti-TNF agents in patients with chronic hepatitis C.

The second scenario is an inflammatory arthritis occurring in the setting of HCV-associated mixed cryoglobulinemia [16]. Cryoglobulins can be detected in approximately half of chronically HCV-infected patients but less than 5% develop the distinct manifestations of the mixed cryoglobulinemia syndrome such as purpura, neuropathy, membranoproliferative glomerulonephritis, and so on [16,17]. An immune-mediated process through the deposition of monoclonal RF or immune complexes containing RF and polyclonal IgG, with or without associated HCV antigens, in small vessel walls in different tissues such as the skin, nerves, synovium, and glomeruli is the presumed pathogenetic mechanism [18]. In the majority of cases, patients with mixed cryoglobulinemia present with intermittent nonspecific polyarthralgias involving the hands and knees whereas less than 10% develop frank nonerosive arthritis. The diagnosis of arthritis in HCV-associated mixed cryoglobulinemia requires the recognition of a combination of clinical (purpura, membranoproliferative glomerulonephritis, peripheral neuropathy, and skin ulcers), serologic (type II or III cryoglobulins, low C4, and positive RF), and histological (leucocytoclastic vasculitis) findings. The treatment of mild to moderately severe HCV-associated mixed cryoglobulinemia includes combination antiviral treatment (pegylated IFN-α + ribavirin) with or without low-dose corticosteroids (prednisone of less than 10 mg/day) [19]. In more severe cases, high-dose corticosteroids, cyclophosphamide, rituximab, and/or plasmapheresis followed by antiviral treatment have been used [20].

In less than 5% of patients with chronic HCV infection, an inflammatory arthritis directly related to HCV has been reported [21]. The pathogenetic role of HCV in these cases has not been proven. Most patients present with an RA-like picture of a symmetric, nondeforming, nonerosive polyarthritis involving predominantly small joints (metacarpo-phalangeals, proximal interphalangeals, and ankles). In approximately 20% of the cases, a mono- or oligo-arthritic pattern is observed. In the reported cases in the literature, approximately 40% were cryoglobulin-positive and 70% RF-positive, making the differential diagnosis from early RA or HCV-associated mixed cryoglobulinemia challenging [21]. The presence of anti-CCP antibodies is helpful for the diagnosis of RA in this setting, but it should be noted that approximately one third of patients with early RA are anti-CCP-negative. There are limited data on the treatment of HCV-associated arthritis; analgesics, low-dose corticosteroids (<10 mg/day), and (rarely) disease-modifying antirheumatic drugs (DMARDs) or anti-TNF agents can be used [21]. Rarely, patients with chronic hepatitis C receiving treatment with IFN-α can develop inflammatory polyarthritis or true RA [12].

Parvovirus B19

Parvovirus B19 is a member of the family of small, nonenveloped, single-stranded DNA viruses *Parvoviridae* and is the cause of the common childhood illness erythema infectiosum as well as of transient aplastic crisis, hydrops fetalis, and bone marrow suppression in immunocompromised patients [22]. The infection is spread by the respiratory route and has a household transmission rate of approximately 50%. Nearly half of the adult population is IgG anti-B19-positive. Of interest is the fact that, in children with erythema

infectiosum, articular disease is uncommon, with joint swelling in less than 3% of those infected under 10 years of age. In adults, however, where the infection commonly occurs in the absence of the characteristic rash, arthralgia is far more common [22]. Symptoms begin in a few joints but rapidly spread, often in an additive fashion. The pattern of joint involvement is RA-like and is accompanied by prominent morning stiffness, thus posing a diagnostic challenge in patients presenting with acute-onset polyarthritis. Further confounding the diagnostic situation is the well-documented occurrence of transient autoantibody formation including RF (generally in low titer), ANAs, anti-DNAs, antibodies against extractable nuclear antigens, and others. Clearly, the constellation of cytopenias, polyarthritis, and ANA or anti-DNA can mimic SLE as well. B19-associated arthritis is self-limited and generally resolves in a few weeks but occasionally lasts much longer. Chronic arthritis secondary to B19 infection has been reported but its causal role in such cases is uncertain [2].

The pathogenesis of B19-associated arthritis is believed to be driven by virus-specific antibody and immune complex formation since articular symptoms seem to coincide with the appearance of B19-specific IgM. Diagnosis is confirmed by the presence of specific IgM antibodies with or without specific IgG, while the detection of IgG alone is consistent only with past infection. Virus can also be detected in serum by polymerase chain reaction (PCR) at such times, although this is not clinically necessary. The issue of major importance in terms of diagnosis is not to confuse B19 infection with early-onset RA [2]. B19 can be detected in the synovium of patients with both RA and osteoarthritis and the significance in these settings, while debated, is not believed to be etiopathogenic [23]. Treatment is generally supportive, although intravenous immunoglobulin (IVIG) has been used successfully to treat chronic B19 infection to allow marrow recovery. IVIG is not recommended in B19-associated arthritis [2].

HIV infection

The epidemic of HIV infection is now over a quarter century old. While globally it is still pandemic, in the industrialized West the disease has been transformed into a chronic, complex, but largely manageable disease for those with access to antiviral drugs and who tolerate multiple-drug therapy commonly known as highly active antiretroviral therapy (HAART). The early days of HIV disease predating the use of HAART (1996 and before) were associated with rich clinical descriptions of nosologically distinct forms of arthritis that at times were clinically severe [24]. These articular syndromes were heterogeneous and are listed in Table 1. In the era of HAART, there has been a transformation in the incidence of associated arthritis with several studies, including the only longitudinal cohort investigation, clearly documenting a significant and dramatic decrease in these complications [25]. In their place are a number of heretofore-undescribed rheumatic disorders; one example of a new nosologic entity is the immune reconstitution syndrome seen with the initiation of HAART in severely immunosuppressed patients [26]. In this syndrome, patients with previously occult opportunistic infections due to mycobacteria or other pathogens, when exposed to HAART, experience a resurgence of their CD4 counts in the peripheral blood and tissues, accompanied by an inflammatory syndrome characterized by fever, lymphadenopathy, and serious end-organ damage. The syndrome is believed to result from the reconstitution of the flagging immune system with a resultant inflammatory reaction to previously occult and clinically asymptomatic infection. While this immune reconstitution syndrome was originally reported in reaction to occult infections, a sterile form that is associated with the appearance of new-onset autoimmune or inflammatory disorders, including arthritis, has also been described [26]. The syndrome is generally self-limited and thus clinically important in terms of not over-treating it. Nonsuppurative rheumatic syndromes continue to be prevalent in areas without access to HAART, including most of Africa and large parts of Asia [25].

Table 1

Arthritic manifestations of HIV infection

Commonly encountered in the pre-HAART era (before 1996)
HIV-associated arthritis
HIV-associated reactive arthritis
Psoriatic arthritis
Painful articular syndrome
Ameliorated by HIV infection but worsening or appearing with HAART
Rheumatoid arthritis
Undifferentiated polyarthritis

HAART, highly active antiretroviral therapy.

Alphaviruses

Inflammatory polyarthritis has long been associated with alphavirus infections but for rheumatologists in the industrialized West these disorders have been little more than curiosities [27,28]. Among the 26 members of the genus, all are arboviruses [4]. Aside from Ross River disease, which infects approximately 9,000 individuals annually and has been intensively investigated, the remaining infectious agents that are all associated with arthritis (Table 2) are endemic to tropical zones and have been less rigorously studied [29].

Over the past 2 years, there has been an epidemiologic shift in at least one of these viruses, Chikungunya virus (CHIKV), which is both clinically fascinating and of clinical importance to global health. CHIKV, like other members of the genus, is a single-stranded RNA virus and is a mosquito-borne infection that in the past has been responsible for significant epidemics in Asia and Africa [27]. In 2006, an outbreak of CHIKV swept over several islands in the Indian Ocean and in parts of India proper. During the same period, increasing

Table 2

Globally distributed arthritogenic alphaviruses

Arthritogenic alphavirus	Geographic distribution	Comments
Ross River	Australia and Oceania	Reported in travelers and visiting US military personnel.
Barmah Forest	Australia	
Sindbis group	Africa, Asia, and Australia	Enzootic vertebrate hosts are birds. Also reported in travelers.
Karelian fever	Russia	
Ockelbo	Sweden	
Pogosta	Finland	
Mayaro	South America	
O'nyong-nyong	Central and East Africa	
Igbo Ora	Central Africa	
Chikungunya	South and East Asia, Africa, West Pacific, and sporadic cases in Europe and the US	Reported in travelers from endemic areas to the US and Europe. Recent mosquito-borne outbreak described in Northern Italy.

numbers of cases were reported in infected visitors returning to Europe and the US [27,30]. An editorial in *The New England Journal of Medicine* in February 2007 noted that the vector for CHIKV has increasingly shifted from *Aedes aegypti* to *Aedes albopictus*, a mosquito widely distributed in the West [31]. The authors postulated that, given that the spread of such vector-borne diseases requires only a host reservoir and a capable vector, globalization of such illnesses is 'only a matter of time' [31]. Only 5 months later, the first reports of a local epidemic of CHIKV in Northwestern Italy were published, with nearly 200 possible cases described and traced to an infected traveler returning home with subsequent spread by *A. albopictus* [32,33].

From the rheumatologic perspective, it is important since nearly all infected patients develop an inflammatory polyarthritis that, while generally short-lived, is clinically severe and may mimic more serious and persistent forms of non-infectious arthritis. The disease has been reported to run through two consecutive phases [30]. During the early phase (<10 days), fever, transient rash (macular, popular, or generalized erythematous located in the trunk), conjunctivitis, myalgias and symmetric polyarthralgias, and/or polyarthritis involving mainly the wrists, hands, ankles, and toes are present [30]. Edema of the face and periarticular tissues is a characteristic clinical finding in these patients. Axial pain is also common, affecting almost half of the patients. During this phase, elevation of liver (AST, ALT, and γ-glutamyl transferase) and muscle (creatine phosphokinase and lactate dehydrogenase) enzymes is observed in 50% of patients, accompanied by cytopenias (thrombocytopenia and leucopenia). In some cases, thrombocytopenia can be severe, causing petechial hemorrhages. During the second stage of the disease (>10 days), most patients have persistent joint complaints in the form of tenosynovitis involving wrists and fingers and/or arthritis involving the proximal finger joints. At this stage, there is no associated fever or rash. Almost half of the patients continue to have articular symptoms 6 months after the onset of disease. Raynaud phenomenon has been reported in approximately 15% of the patients [30]. Laboratory work-up is normal during this phase. Only symptomatic treatment with analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) is given through the entire course of the disease since no specific therapy is available. In certain cases, short courses of corticosteroids were administered for symptomatic relief.

Another arbovirus, West Nile virus, has clearly demonstrated to all Western physicians the significance of living in a global village. Familiarity with such illnesses among Western physicians is now justified as well as the need for entomologic surveillance, public education, and early detection of imported and locally transmitted cases as well as vector control.

The diagnosis of alphavirus infection requires the identification of specific IgM antibodies (by enzyme-linked immunosorbent assay) and/or virus isolation by virus neutralization assays or PCR [34]. For CHIKV infection, detection of viral RNA should be performed during the first week of illness when high-titer viremia is present. Testing for CHIKV is available through the Centers for Disease Control and Prevention [35] and recently has been commercially available in the US.

Human T-cell lymphotropic virus type I

Human T-cell lymphotropic virus type I (HTLV-I), a human retrovirus, is an established cause of inflammatory arthropathy in endemic areas such as Southern Japan and the Caribbean [36]. The virus is being transmitted perinatally, sexually, and through contaminated blood transfusion. Patients with HTLV-I-associated arthropathy, usually elderly women, present with the typical picture of a symmetric inflammatory arthritis not much different from RA. RF is frequently detected while x-rays of the affected joints reveal mild erosive changes and thus its overall prognosis is considered better than that of RA. NSAIDs, DMARDs, and low-dose prednisolone have been used for the treatment of the arthritis [36].

Other viruses

Rarely, other viruses, including rubella virus [37], EBV [38], and coxsackie virus [39], have been implicated as causes of

Table 3

Features of the most common virus-associated arthritides

		HCV					
Virus	HBV	HCV-associated arthritis	HCV-associated mixed cryoglobulinemia syndrome	HIV	Parvovirus	Alphaviruses	HTLV-I
Epidemiology							
Population at risk	- IVDUs - Persons with multiple sexual partners - Health workers	- IVDUs - Transfusion before 1992 - Persons with multiple sexual partners - Health workers		- IVDUs - Persons with multiple sexual partners	- Workers at schools or day care facilities	- Travelers or inhabitants of endemic areas (Africa, South and Southeast Asia)	- Perinatal - Sexual transmission in endemic areas (Caribbean, Japan)
Clinical findings							
Type of joint manifestations	Polyarthritis	Polyarthritis (80%), mono-/oligo-arthritis (20%)	Polyarthralgias	Oligoarthritis	Polyarthritis	Polyarthritis	Polyarthritis
Duration of arthritis	2 to 3 weeks	Chronic	Chronic	Chronic	2 to 3 weeks	Weeks to months	Chronic
Characteristic extra-articular manifestations	- Generalized skin rash - Fever - Myalgias		- Purpura - Peripheral neuropathy - Glomerulonephritis - Skin ulcers		- Prodromal phase lasting 1 week with flu-like symptoms prior to arthritis - Skin rash (<20% 'slapped cheeks')	- Fever - Skin rash - Myalgias - Headache - Nausea	- Vasculitis - Sjögren-like syndrome
Laboratory findings							
Diagnosis of associated viral infection	HBsAg (+) Anti-HBc IgM (+) ↑↑ ALT/AST	Anti-HCV (+) (EIA) and HCV RNA (+) (PCR)		Anti-HIV (+) (ELISA) and HIV RNA (+) (PCR)	IgM B19 Ab (+)	Specific IgM Abs (+) and viral RNA (+) (PCR)	Anti-HTLV-I (+) (ELISA) and Western blot or HTLV-I DNA (+) PCR
RF	25% (+)	40% to 70% (+)	>90% (+)		Rarely (+)	Negative	(+)
Other		Cryoglobulins: 40% (+)	Cryoglobulins: 100% (+) Low C4: 50% to 85%				
X-ray findings							
Erosive disease	No	No	No	Rarely	No	No	Yes
Therapy							
a. Antiviral	Not needed	Peg-IFN-α + ribavirin × 6 to 12 months		HAART	Not needed	Not available	Not available
b. Treatment for the joint manifestations	- Analgesics	- Analgesics - Low-dose prednisone - DMARDs (rarely) - Anti-TNF (rarely)	Mild-moderate disease: - Low-dose prednisone Severe disease: - High-dose steroids - Cyclophosphamide - Rituximab ± plasmapheresis	- Analgesics - NSAIDs - DMARDs (in severe cases and only if CD4 >200 mm^3) - Anti-TNF (in severe cases and only if CD4 >200 mm^3)	- Analgesics	- Analgesics - NSAIDs	- NSAIDs - Corticosteroids - DMARDs

Ab, antibody; ALT, alanine aminotransferase; anti-TNF, anti-tumor necrosis factor; AST, aspartate aminotransferase; DMARD, disease-modifying antirheumatic drug; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HTLV-I, human T-cell lymphotropic virus type I; IFN-α, interferon-alpha; IVDU, intravenous injection drug user; NSAID, nonsteroidal anti-inflammatory drug; PCR, polymerase chain reaction; RF, rheumatoid factor.

acute self-limited arthritis. For some of these viruses, especially EBV, a triggering role for the development of chronic inflammatory arthritis (that is, RA) has been proposed, but no definite link has been established so far [40].

Differential diagnosis – whom to screen

In Table 3, the pertinent epidemiological, clinical, laboratory, and x-ray findings as well as the treatment choices for the most common viral-associated arthritides are illustrated. Although a number of viruses can cause different arthritic syndromes, mainly in the type of an RA-like inflammatory polyarthritis, their significance as etiologic factors of arthritis in daily practice is probably limited. In a recent study of 322 French patients presenting with recent-onset polyarthralgias or inflammatory arthritis (<1 year in duration), Zerrak and colleagues [41] identified only two patients (0.6%) whose arthritis could be directly attributed to viral infections (one case with HCV and one case with parvovirus B19). Similar results were obtained in 60 Finnish patients presenting with acute reactive arthritis, of whom only 3% had evidence of recent parvovirus B19 infection [42].

These findings indicate that the search for the above-mentioned viruses should be targeted to specific patient populations presenting with articular symptoms. High-risk groups include intravenous injection drug users, persons who had been transfused with blood or blood-derived products prior to 1992, persons with multiple sexual partners, health care workers with frequent needle-stick injuries or exposure to blood, workers at schools or day care facilities, and travelers or immigrants from endemic areas for alphaviruses or HTLV-I infection (Table 3).

Conclusion

Although viruses are responsible for only a small proportion of all cases of acute or chronic arthritis in daily practice, rheumatologists in 2008 should be aware of the key clinical manifestations and the laboratory tests that are needed for their diagnosis. The diagnosis of a virus-associated arthritis is important for several reasons. The identification of a virus as a responsible agent for arthritis can limit unnecessary diagnostic work-up and prevent the initiation of a potentially harmful chronic immunosuppressive therapy. It can also help to identify patients with chronic viral infections such as HCV or HIV for whom antiviral therapy could be life-saving. Lastly, for emerging viral infections such as those caused by alphaviruses, an early diagnosis has obvious epidemiological and public health implications.

Competing interests

The authors declare that they have no competing interests.

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