Pathogenesis and diagnosis of viral arthritis

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INTRODUCTION — Arthritis and arthralgias are well-recognized and relatively common accompaniments to viral infections. The most common viruses causing arthritis and arthralgias are parvovirus, hepatitis B, hepatitis C, rubella, and the alphaviruses [1]. Joint complaints are also observed less commonly in association with a wide variety of other viral infections (eg, mumps, enteroviruses, herpesviruses) (table 1) [1].

This topic will provide a general overview of the pathophysiology, presentation, diagnosis, and treatment of viral arthritis. Specific viruses that cause arthritis are discussed separately. (See "Specific viruses that cause arthritis".)

PATHOPHYSIOLOGY — No virus has been implicated as a cause of the common forms of chronic inflammatory arthritis such as rheumatoid arthritis or systemic lupus erythematosus. However, viruses are able to initiate rheumatic symptoms via a variety of different mechanisms. Viruses may cause effects through numerous mechanisms that depend on host factors, including age, gender, genetics, infectious history, and immune response [1-5].

Direct invasion — Viruses may directly invade the joint, resulting in infection of the synovium or other joint tissues. This may be the mechanism utilized by rubella and rubella vaccine virus despite the fact that viral isolation from a joint is a rare occurrence [6-11]. In vivo data support the tropism of these viruses for synovial tissue and their potential for both lytic and persistent infection. Other viruses that may be arthrotropic include parvoviruses [12] and enteroviruses [13]; both of these have been successfully isolated from joint fluid.

Immune complex formation — Viral particles (either whole virions or viral antigens) may act as the antigenic component of immune complexes formed by the humoral response to viral infection [1,2,12,14]. These immune complexes may be preferentially deposited in the joints and skin, leading to arthralgias, arthritis, and rash. This type of presentation is common and has been well-documented in the cases of hepatitis B infection, alphaviruses, hepatitis C (often via the formation of cryoglobulins), and parvovirus. Antibodies directed against viral antigens also may crossreact with tissue antigens, a process called molecular mimicry [3,4].

Latent viruses and immune dysregulation — Viruses may establish persistent infections in which the host cells remain metabolically active, expressing viral antigens on their cell surfaces [15,16]. These antigens become a target for the immune system, resulting in the development of chronic inflammatory reactions. This situation has not been documented to occur in synovial tissues in man but has been seen with lentivirus infection in animals in which it gives rise to a chronic form of caprine arthritis [17].

Viruses may also directly infect elements of the immune system [18]. This can lead to a primary immunologic derangement, which could eventually produce signs or symptoms of autoimmunity and rheumatic disease.

Also, in many patients with autoimmune disease, a potential complication of immunosuppressive therapy is reactivation of pathogenic viruses that have remained latent. The most commonly encountered are varicella-zoster virus, hepatitis B and C, Epstein-Barr virus, and polyoma JC virus [19]. Many cases of reactivation of Epstein-Barr infections have been seen in patients with rheumatoid arthritis or juvenile idiopathic arthritis on biologics such as the TNF inhibitors or rituximab.

CLINICAL PRESENTATION — Patients with viral arthritis tend to present with symmetric polyarticular disease that may consist of arthralgias alone or a true arthritis that can mimic a rheumatic disease. In general, the musculoskeletal signs and symptoms are seen during the prodrome of, or coincident with, the clinical onset of infection. Joint involvement tends to be of sudden onset and of relatively short duration and may be accompanied by a rash.

Arthralgias and arthritis generally do not persist or recur in the vast majority of cases of viral arthritis. Exceptions to this rule have been reported with infections due to rubella virus, parvovirus, and alphavirus [9-12]. Even in instances of persistent or recurrent symptoms, however, viral arthritis has not been shown to lead to persistent chronic arthritis and destructive joint disease.

DIAGNOSIS — Establishing or even suspecting the diagnosis of viral arthritis varies with the clinical setting. In some patients, the diagnosis may be strongly suspected on clinical grounds because of a classic rash (rubella), facial rash (parvovirus), physical finding (parotid enlargement in mumps or jaundice in hepatitis B or hepatitis C virus infection), or historical feature (onset after rubella vaccination). In many cases, however, the diagnosis of viral arthritis is made difficult by the following features:

- There is no single presentation that is typical of viral arthritides.
- Many of the signs and symptoms are general in nature (fever, arthralgia, rash) and can be seen in several different types of disorders.
- Arthritis may occur before the onset of the major signs of the viral infection (eg, before icterus in hepatitis B virus infection).
- Evidence of viral infection (viral isolation or serologic evidence of recent infection) is difficult to document.

As a result, there are two components to the diagnostic approach to viral arthritis: establishing the diagnosis when it is suspected (which usually begins with serologic testing), and evaluating the patient with polyarticular joint pain when a specific viral infection is not suspected.

Serology — Serologic testing is the most common means of establishing a viral etiology for a clinical condition. Serologic diagnosis is based upon two facets of the immune system's response to viral infections: the first exposure to an agent results in the development of an initial IgM response, and the IgM response is followed by isotype switching and by the appearance of IgG antibodies. Thus, if viral infection is suspected, serum should be collected immediately and then approximately two to three weeks later. Serologic testing must be directed against the specific viruses suspected to be involved based upon both epidemiologic and clinical data.

- An acute IgM antibody response followed by the presence of IgG antibodies against the suspected agent confirms a viral etiology.
- A significant (greater than fourfold) time-related increase in IgG also suggests a recent infection in which the initial sample was obtained too late to detect the IgM response. Alternatively, this serologic pattern could represent reinfection with a particular virus or recrudescence of infection.
- The presence of a stable level of IgG antibody is not diagnostic of recent infection since it may represent a viral infection that significantly antedated the onset of arthritis.

Immunoassays for both IgM and IgG antibodies to a variety of viral components have replaced the older classical means of serologic diagnosis. Direct testing of serum for viral-specific nucleic acid by polymerase chain reaction (PCR) can also be performed.

Viral isolation from the joint — Strict confirmation of a viral etiology of an arthritic condition requires isolation of the etiologic agent from the site of musculoskeletal symptoms (joint fluid or synovium). Any isolate from the joint can be considered pathogenic since the joint does not harbor known persistent viruses. Care must be exercised, however, not to culture blood elements as a consequence of a traumatic aspiration or as part of the synovial material that is biopsied. Synovial biopsy for possible viral isolation should be performed in clinical practice in patients with persistent synovitis of unknown etiology that has not responded to medical therapy.

The following viruses have been isolated from joint fluid or synovium in individuals with clinical signs of arthritis: rubella virus, rubella vaccine virus, parvovirus, enterovirus, vaccinia virus, and herpes family viruses [1,11,17]. (See "Specific viruses that cause arthritis".) In addition to isolation of the virus, identification of viral nucleic acid by PCR is another method to confirm viral infection of the joint. PCR may be helpful in selected cases but is difficult to use as a screening tool.

However, only a small number of viruses directly infect the joint, and viral isolation in these cases is accomplished infrequently. Thus, other means must be employed to make the diagnosis of viral arthritis.

Viral isolation from other tissues — Viral cultures from other parts of the body can be attempted. For cases in which viral isolation is unequivocally pathogenic (eg, rubella and arthropod-borne alphaviruses), identification of the virus represents strong presumptive evidence for the etiology of the associated joint symptoms. In contrast, one cannot unequivocally relate joint symptoms with the isolation of commonly found organisms (eg, enteroviruses from the stool or Epstein-Barr virus from the blood or saliva). In clinical practice, this would only be performed in patients with persistently active disease of unknown etiology despite other testing.

Other laboratory tests — Other laboratory tests have been of little value in differentiating viral arthritis from other musculoskeletal conditions.

- There is usually little change in the white blood cell count, although some viral infections are associated with either a mild leukocytosis or lymphopenia.
- Liver function tests may be elevated with infections due to viruses that have tropism for the liver (eg, hepatitis B and C viruses, parvovirus, and Epstein-Barr virus).
- Complement levels are not of diagnostic utility, although low levels may be seen with immune complex deposition diseases. Essential mixed cryoglobulinemia, which is associated with both arthritis and hypocomplementemia, is most often due to hepatitis C virus infection. (See "Clinical manifestations and diagnosis of the mixed cryoglobulinemia syndrome (essential mixed cryoglobulinemia)".)
- Detection of viral DNA in synovium or synovial fluid is an attractive approach in theory, but, in practice, high rates of detection of viral DNA sequences in controls (eg, 50 percent and 21 percent for parvovirus B19 in synovium and synovial fluid, respectively, of controls with osteoarthritis [20]) have limited usefulness of PCR in clinical practice.

Synovial fluid analysis — Evaluation of synovial fluid is of limited utility in the diagnosis of viral arthritis except for the occasional positive culture. The synovial leukocyte counts may be elevated, occasionally to quite high levels; however, normal cell counts are not uncommon. There may be a predominance of polymorphonuclear leukocytes or lymphocytes, depending upon the viral etiology. Most importantly, the synovial fluid should always be cultured for bacteria and other organisms as well as viruses, in order to detect a potentially treatable disorder.

Approach to the patient with polyarticular joint pain — The patient in whom there is no obvious association with a particular viral infection must be evaluated for the multiple other causes of polyarticular joint pain (table 2). This topic is discussed in detail separately. (See "Evaluation of the adult with polyarticular pain".)

A possible viral etiology should be considered in patients with synovitis of less than six weeks' duration and in those with polyarthralgias without synovitis. Complete blood count (CBC), urinalysis, erythrocyte sedimentation rate, C-reactive protein, and comprehensive metabolic panel including liver function tests and muscle enzymes should be obtained in all such patients, along with testing for rheumatoid factor, anticyclic citrullinated peptide antibodies, and antinuclear antibody profiles to help rule out rheumatoid arthritis or a systemic rheumatic disease. Serologic testing for hepatitis B and C virus, parvovirus, and Epstein-Barr virus infection should be considered in any child or adult patient in whom the etiology of their synovitis is unclear despite initial routine testing.

TREATMENT — Therapy in viral arthritis is generally directed at relief of symptoms and at maintenance of function. Patients should be treated with analgesic agents (eg, acetaminophen) and nonsteroidal antiinflammatory drugs in doses typically used in any inflammatory arthropathy. Physical and occupational therapy can be initiated if required to maintain or improve function.

The use of glucocorticoids, either orally or by intraarticular injection, should be discouraged since they are of limited utility in this disorder. Use of glucocorticoids may mask the disease and the correct diagnosis.

There is no need for specific antiviral therapy since most viral arthritides are of short duration and are self-limited. This is fortunate because no specific antiviral therapy exists for most of the agents implicated in causing rheumatic disease. One exception is interferon-alpha for hepatitis C virus-induced mixed cryoglobulinemia. (See "Treatment of the mixed cryoglobulinemia syndrome (essential mixed cryoglobulinemia)".)

SUMMARY AND RECOMMENDATIONS

- The most common viruses causing arthritis and arthralgias are parvovirus, hepatitis B, hepatitis C, rubella, and the alphaviruses, as well as Epstein-Barr virus infections in patients on biologics. Joint complaints are also observed less commonly in association with a wide variety of other viral infections (eg, mumps, enteroviruses, herpesviruses) (table 1). (See 'Introduction' above.)
- Viruses are able to initiate rheumatic symptoms via a variety of different mechanisms that depend upon host factors, including age, gender, genetics, infectious history, and immune response. Major mechanisms include the direct invasion of the joint (eg, rubella and enteroviruses) and immune complex formation, which may occur both in the joints and in the skin (eg, hepatitis B and C, alphaviruses). Parvovirus may use both of these mechanisms. Molecular mimicry may also occur. (See 'Pathophysiology' above and 'Direct invasion' above and 'Immune complex formation' above.)
- The usual presentation includes the sudden onset of symmetric polyarticular arthralgias or arthritis, sometimes associated with a rash. The musculoskeletal manifestations are typically seen during the prodrome of, or coincident with, the clinical onset of infection. Articular manifestations generally do not persist or recur, except with infections due to rubella virus, parvovirus, and alphavirus. Viral arthritis has not been shown to lead to persistent chronic arthritis and destructive joint disease even when symptoms persist or recur. (See 'Clinical presentation' above.)
- The two components to the diagnostic approach to viral arthritis are establishing the diagnosis when it is suspected (which usually begins with serologic testing) and evaluating the patient with polyarticular joint pain when a specific viral infection is not suspected. Signs and symptoms are usually nonspecific, and clinical evidence of a specific viral etiology on exam may occur but is uncommon. Thus, if viral infection is suspected, serum should be collected immediately and then approximately two to three weeks later to detect the IgM antibody response seen with exposure to the agent and the switch to an increasing IgG response. Serologic testing must be directed against the specific viruses suspected to be involved based upon both epidemiologic and clinical data. Other laboratory tests have been of little

value in differentiating viral arthritis from other musculoskeletal conditions. (See 'Diagnosis' above and 'Serology' above and 'Other laboratory tests' above.)

- We consider a possible viral etiology in patients with synovitis of less than six weeks' duration and in those with polyarthralgias without synovitis. Our initial evaluation in all such patients includes a complete blood count (CBC), urinalysis, erythrocyte sedimentation rate, C-reactive protein, and comprehensive metabolic panel including liver function tests and muscle enzymes. Serologic testing for hepatitis B and C virus, parvovirus, and Epstein-Barr virus infection should be performed in any child or adult patient if the etiology is not established with routine testing. Testing for rheumatoid factor, anticyclic citrullinated peptide antibodies, and antinuclear antibodies should be performed to rule out rheumatoid arthritis or a systemic rheumatic disease. (See 'Approach to the patient with polyarticular joint pain' above.)
- Therapy is generally directed at relief of symptoms and at maintenance of function by use of analgesic agents (eg, acetaminophen) and nonsteroidal antiinflammatory drugs in antiinflammatory doses; physical and occupational therapy can be initiated if required to maintain or improve function. We generally avoid the use of either oral or intraarticular glucocorticoids. (See 'Treatment' above.)