Chapter 3

Viral Arthritis; Covid19 Update

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Summary

Viral arthritis is a self-limiting and non-destructive arthritis that occurs during or after various viral infections. The pathogenesis of viral arthritis is still not fully understood, but mechanisms such as direct invasion of synovial cells, immune complex formation and molecular mimicry (imitation) are emphasized. All over the world, the most common viruses causing arthritis are Parvovirus B19, Rubella, hepatitis B and hepatitis C virus and alphaviruses, and viruses such as Zika and Chikungunya are tropical viruses that cause arthritis in endemic areas. In addition, during the Covid -19 pandemic, which has been affecting the whole world since 2019, it has been determined that the SARS-CoV-2 virus also causes musculoskeletal symptoms such as arthritis and arthralgia. Many viral arthritis usually begin with nonspecific symptoms seen in viral infections. Joint involvement can be in different patterns. Although no major abnormality is usually observed in routine laboratory tests, they can sometimes lead to positivity of autoantibodies such as ANA, RF, Anti-ds DNA and ANCA. In addition, although it is usually a self-limiting form of arthritis, arthritis may become chronic, especially in immunodeficiency or in the presence of chronic persistent infection. Chronic rheumatic disease may be misdiagnosed in cases of long-lasting viral arthropathy. Viral infection may also be a triggering factor in the etiology of chronic rheumatic disease. It is important to make the differential diagnosis of viral arthritis, as the treatment modalities between the two disease groups are different.

INTRODUCTION

Viral arthritis are acute and self-limiting diseases. Viral arthritis is accompanied by fever, distinctive skin manifestations, hematological abnormalities, particularly in parvovirus B19, and other clinical features. Including parvovirus B19 chronic polyarthritis mimicking rheumatoid arthritis (RA) in adults, polyarthritis may occur also in other virus infections. It is necessary to know the epidemiology of viral infections and to perform laboratory examinations appropriate to the disease process for diagnosis. Different viruses can cause arthritis in a host by various mechanisms (immune complex

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formation, direct invasion of synovial cells, and others). The most common arthritogenic viruses worldwide are some tropical viruses such as Parvovirus B19, Hepatitis B virus - hepatitis C virus (HBV - HCV), Rubella, human immunodeficiency virus (HIV), Zika virus, Alphaviruses, and Chikungunya virus (CHIKV) [1-3]. In the COVID-19 pandemic that started in 2019, the association of arthralgia and arthritis has been described after Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection [4, 5].

Most viral arthritis starts with nonspecific symptoms. There is headache, malaise, chills, fatigue, neck stiffness, nausea-vomiting, fever, sore throat, often macular or papular rashes. Mild fever and regional lymphadenopathy (LAP) may also be the only extra-articular finding. The absence of a single pattern of joint involvement is characteristic. In hepatitis B alone, the arthritis can be symmetrical, asymmetrical, migratory, or appended. Morning stiffness is usually in the affected joint. On the other hand, arthralgia may be the only manifestation of involvement [1, 6]. Routine laboratory tests usually show few abnormalities. Some patients may have a mild anemia or a few atypical lymphocytes. Rheumatoid factor (RF) is usually negative except for Rubella. Antinuclear antibody (ANA) is negative. High erythrocyte sedimentation rate (ESR) is the most common abnormality. Patients with hepatitis B may also have cryoprecipitates and decreased serum complement levels in their serum. Synovial fluid studies are nonspecific and reflect varying degrees of inflammation. The general finding is a high white blood cell (WBC) count of 15000-25000 mm3, which is typical for rheumatoid arthritis (RA) and the predominant cell type is polymorphonuclear cell (PMN) [1-3, 6].

Little is known about how viruses induce arthritis (except for hepatitis B and hepatitis C, where immune complex- mediated pathogenesis is concerned). It has been shown that the virus can be replicated in the synovium by obtaining the virus from the synovial fluid of many patients in rubella. Since many findings are nonspecific, "how to recognize viral arthritis" or "how to suspect?" questions can be considered. Information on exposure is helpful in this regard. Conditions such as iv. drug use for hepatitis B, new immunization for rubella, history of going to an endemic area, seasonal onset for arboviruses and enteroviruses provide clues for diagnosis. However, the most well-known characteristic feature of viral arthritis is that they are of short duration. The short duration of arthritis without deforming changes is the major difference between known types of viral arthritis and RA. However, recent studies sometimes blur this distinction. Hepatitis B arthritis can last for months and can lead to vasculitis indistinguishable from polyarteritisnodosa (PAN). Direct radiographs of the affected joints may show progressive osteoporosis (OP) and significant loss of articular cartilage. Rubella arthritis with rubella virus vaccine (HPV77, DK12) may recur in as long as

three years, but each attack is short-lived. In addition, some reports indicate that the rubella virus causes chronic erosive arthritis. It is also stated that rubella, mumps and coxsackie viruses are associated with a condition similar to Still's disease [7]. Although viral arthritis is mostly self-limiting and non-destructive, chronic form may develop in two cases. The first of these occurs when immunocompromised patients become infected with the agent. A short-term infectious agent in the normal host can lead to chronic and recurrent infection in immunodeficiency and cause chronic viral arthritis. In the second case; Chronic viral arthritis may develop in infections of the nature of chronic persistent viral disease [6,7]. In the development of viral arthritis, besides host factors such as age, genetic predisposition and immunity, viral factors such as virus tropism, replication feature, ability to cause persistent infection, cytopathic effect, viral expression feature similar to host antigens and viral factors also play a role, for instance the ability to alter the host's immune response. [8, 9].

VIRUSES CAUSED ARTHRITIS

Distinct Arthrogenic Viruses

- Parvovirus B19
- Hepatitis B and C virus
- Rubella virus and vaccine
- Mumps virus
- HIV-1
- Human T-lymphotropic virus-1 (HTLV-1)
- Lymphocytic choriomeningitis virus (LCMVr) .
- Alpha Viruses

  Chikungunya virus

  O'nyong-nyong virus

  Igbo-ora virus

  Ross-River virus (Australia's epidemic polyarthritis)

  Sindbis virus

  Mayaro virus

Rarely Arthrogenic Viruses

- Adenovirus

- Herpes Viruses (Herpes Simplex virus type-1 (HSV-1), Epstein-Barr virus (EBV), Varicella Zoster virus (VZV), Cytomegalovirus (CMV))
- Rubeola
- Enteroviruses (Coxsackie virus, ECHO virus type 6-9, Hepatitis A)

FINDINGS ACCOMPANYING VIRAL ARTHRITIS

In addition to general symptoms such as sore throat, nausea-vomiting, myalgia, chills, malaise in hepatitis B infection; urticarial, macular, papular, petechial rashes, lymphadenopathy and low-grade fever may occur [7].

In rubella, flu, cough, sore throat, myalgia, malaise, as well as morbiliform eruptions, LAP and low-grade fever are seen. In cases of rubella vaccine-induced arthritis, colds, cough, sore throat, morbiliform rashes, LAP and low-grade fever may accompany [8].

Adenovirus may present with sore throat, maculopapular skin lesions, low-grade fever, pericarditis, and meningitis. In Varicella Zoster infection, malaise, vesicular skin lesions, and fever may occur. Vesicular skin lesions are seen in HSV-1. Epstein–Barr Virus infection often progresses with headache, malaise, sore throat, maculopapular rash and LAP. Coxsakie virus can progress with sore throat, pleuritic pain, maculopapular rash, fever, myopericarditis. Echovirus Type 6-9 can progress with fever, sore throat, vomiting headache, macular skin lesions, fever and meningitis [3, 7, 10].

MUSCULOSKELETAL INVOLVEMENT IN VIRAL ARTHRITIS

The rate of development of arthritis during hepatitis B infection is 10-30%. The duration of arthritis varies between 7-180 days. Joint involvement can be symmetrical, migratory or additive. Sometimes large joints can also be seen in the form of tendinitis or bursitis. The rate of development of arthritis in rubella is 15-35%, and arthritis is more common in adult women and rarely in children and men. The type of involvement is symmetrical, knees, wrists, proximal interphalangeal joints (PIF), carpal tunnel syndrome (CTS), tendinitis, and the mean duration of arthritis is 5-30 days. Rubella vaccine (HPV-77, DK12) induced arthritis is more common in women and affects 1-10% of children. The type of involvement is symmetrical (PIF joints) or monoarticular (knee) and CTS. The average duration of arthritis is 7-21 days. Chikungunya virus causes arthritis in the majority of cases, especially in large joints such as the knees and sometimes in small joints. Chikungunya virüs recurrence can be seen in 5-7th months. Epidemic polyar-

thritis affects most adults and can be symmetrical, sometimes asymmetrical or additive. It occurs in the form of tendinitis and periarticular swelling in the joints, and can last for an average of 14-21 days and sometimes months. Mumps virus causes arthritis at a rate of 0.4% and lasts an average of 14(2-90) days. The type of involvement is in the form of large and small joints and tenosynovitis. Adenoviruses can cause large and small joint arthritis and can show recurrence in 7-35 days. VZV, HSV-1 and CMV mostly involve large joints such as the knee. Coxsackie virus and ECHO viruses can affect large and small joints [3, 6, 7].

LABORATORY FINDINGS IN VIRAL ARTHRITIS MATERIAL

In hepatitis B, an average of 25000 leukocytes per cubic millimeter are detected and the dominant cell type is polymorphonuclear (PMN) cell type. There is no virus culture, but HBsAg can be detected. Limited mononuclear infiltrate may be seen in the synovium. The leukocyte count in rubella is 30000 per cubic millimeter and the dominant cell type is mononuclear cells or PMN cells. Rubella has a cell culture, synovial hyperplasia, increased vascularity and mononuclear cells are detected in the synovium. In epidemic polyarthritis, the mean leukocyte count is 10000 and mononuclear cells predominate. In mumps, there is PMN cell dominance. Similarly, PMN cells and mononuclear cell dominance are observed in adenovirus infection. In Varsella Zoster, the leukocyte count is approximately 4000 and mononuclear cells are dominant. In herpes simplex-1 infection, the leukocyte count is on average 10000 and mononuclear cells are dominant. Epstein Barr virus, CMV and Coxsakie virus are the most common cells in PMN. In echo virus type 6-9, PMN and mononuclear cell dominance is present [6-10].

Autoantibodies detected in peripheral blood in viral infections: Parvovirus B19 has antinuclear antibody (ANA), rheumatoid factor (RF), antineutrophil cytoplasmic antibody (ANCA), Anti-double-stranded (ds) DNA antibody (Anti ds –DNA). Alphaviruses have RF and ANA, rubella has RF, EBV has RF and anti ds-DNA, anti-collagen and anti- cyclic citrullinated peptide (anti-CCP) antibodies. RF and ANA may be positive in HCV, RF and ANA may be positive in HBV, RF and ANA may be positive in HTLV_1 and ANA may be positive in HIV [8-10].

CLINICAL PRESENTATIONS

COVID-19 INFECTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has caused a pandemic that started in December 2019 and affected the whole world. Since the disease started in 2019, it has been named as Coronavirus disease-19 (Covid-19). Symptoms are mild to moderate in most patients, but in about 15% of cases, they progress to acute respiratory distress syndrome, severe pneumonia, multiple organ failure, and septic shock. This pandemic has caused more than 3 million deaths all over the world [11]. While the respiratory infection pathogenesis of SARS-CoV-2 was being investigated all over the world in the midst of the epidemic , there has also been an increasing interest in the immune-mediated consequences secondary to the virus [12]. Patients with a procoagulant state in Covid-19 infection and an inflammatory cytokine storm similar to that in macrophage activation syndrome constitute the most severe cases [13, 14]. A dysregulated hyperimmune response can lead to deepening of damage and autoimmune diseases in susceptible individuals. Many autoimmune diseases have been described in the literature after Covid-19 infections. [15-17].

The pathogenesis of viral arthritis is still only partially understood. One of the known mechanisms in this regard is molecular mimicry. The virus causes autoimmune diseases in susceptible individuals through molecular mimicry [18-20]. Molecular mimicry has also been found for SARS-CoV-2 20. This hypothetically plays a role in the pathogenesis of virus-related immune outcomes that develop both during and after acute systemic infection [21-23]. Guillain Barre syndrome and Miller–Fischer syndrome, which occur through molecular mimicry after Covid-19 infection, have been reported. The mimicked epitopes are also present in the synovial membrane, and acute local inflammation occurs by a similar mechanism [24, 25].

Ibanez et al. conducted a literature review on arthritis after Covid-19 infection for a 1-year period during the epidemic. They reached 30 articles on this subject and after excluding arthritis that may be due to other etiologies, the remaining 3 cases were discussed. The low prevalence of Covid-19-associated arthritis has been attributed to the use of hydroxychloroquine and corticosteroids, which are used in the cure of Covid-19 and also prevent or reduce inflammatory joint manifestations. The features that emerged in the examination of the remaining 3 cases were reported as follows: The time between the onset of arthritis and SARS-CoV-2 infection is variable, but occurs days after acute viral infection and often during the recovery period.

It mostly affects men and occurs as mono or oligoarthritis in the lower extremities. All patients with suspected post-Covid arthritis respond fully and rapidly to non-steroidal anti-inflammatory drugs (NSAIDs) and/or glucocorticoids. As a result, in the pathogenesis based on molecular mimicry, the condition that reveals joint inflammation is the antibody response against the virus. The rapid reduction of immunity within weeks after Covid-19 causes joint manifestations to fade. In addition, this pathogenetic hypothesis regarding immune system hyperactivation reveals why arthritis occurs in those with severe infections and that joint involvement is subclinical in milder infections [26].

Enginar AU. reported 2 cases of arthritis developing in the hand joints after Covid-19 vaccine and fully responding to glucocorticoid treatment [11]. There are reports of elbow arthritis 1 week after SARS-CoV-2 vaccination [27] and reactive arthritis cases developing 1 week after inactive vaccine [28]. Watad et al. reported 27 cases with immune disease attack or new onset of disease after vaccination. Most vaccines are m-RNA vaccines. 21 patients had a previous autoimmune or rheumatic disease. Disease exacerbation was detected in 17 patients, and new-onset immune disease was detected in 10 patients. Among these patients, polymyalgia rheumatica, myasthenia gravis, arthritis, and skin manifestations were found [29]. Watanabe et al. They reported cases of inflammatory bowel disease, new-onset rheumatoid arthritis, anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis, and adult-onset Still's disease after Covid-19 vaccine [30]. Ono et al. They reported a case of reactive arthritis presenting with arthritis and mild Achilles enthesitis of the ankles 21 days after SARS-CoV-2 infection [31]. On the subject, it is clear that more research is needed to understand the pathogenesis of the different clinical phenotypes of Covid-19 infection.

PARVOVİRÜS B –19

Parvovirus B19 is the smallest known DNA virus from the Parvoviridae subfamily and the Erythrovirus genus. This virus replicates autonomously in erythroid precursor cells. It is transmitted by respiratory secretions. Most infections are asymptomatic or in the form of undiagnosed nonspecific viral disease. Approximately 60% of adults have positive serology of a previous parvovirus B19 infection. Its appearance is usually late winter and spring[1]. The disease is defined by its characteristic three-stage rash. Stage 1 is the stage that consists of a bright red rash on the face and includes the image of "slapped cheek". In stage 2, lasting several days to weeks, "lace-like" eruptions spread to the extensor surfaces of the arms, buttocks, and legs. In stage

3, lesions show recurrence in a period of up to 10 months [7]. Parvovirus B19 virus may cause aplastic crisis on the basis of chronic hemolytic anemia. Parvovirus B19 infection may cause recurrent anaemia, thrombocytopenia or leukopenia in immunocompromised patients receiving chemotherapy for lymphoproliferative diseases, or in patients with AIDS. About 5% of children aged 10 years and younger develop arthralgia and 3% develop joint swelling. Joint pain and swelling in adolescents are 12% and 5%, respectively. However, in adults aged 20 years and older, joint pain and swelling are observed in 77% and 60%, respectively. Joint involvement is more common in women. The pattern of acute B19 arthropathy is different in children and adults. Asymmetric and pausiarticular involvement is seen in children. Joint involvement in adults is an RA-like picture with marked symmetrical involvement of the proximal interphalangeal joint (PIF), metacarpophalangeal (MCP), knee, ankle, and wrist. It is a symmetrical polyarthritis most often of acute onset, of moderate severity, that frequently begins on the hands and knees and spreads to the wrists, feet, elbows, and shoulders within 24-48 hours. Joint manifestations are usually self-limiting in adults. However, in a small proportion of adults, the findings can be seen as one of two patterns. In approximately 2/3 of the patients, the findings are seen as arthralgia with intermittent exacerbations and additional morning stiffness. In the other 1/3 patients, the patient is asymptomatic between exacerbations. Rheumatoid factor may be positive at low or moderate titers and often disappears. In the case of chronic disease, B19 arthropathy has been reported to last up to nine years [7, 32].

Molecular mimicry, activation of antigen-presenting cells and viral persistence are emphasized as mechanisms of arthropathy. Parvovirus B19 infection may also be associated with immune-mediated syndromes. These; juvenile rheumatoid arthritis, rheumatoid arthritis, reactive arthritis, Remitting Seronegative Symmetrical Synovitis with Pitting Edema (RS3PE), Systemic lupus erythematosus (SLE), Still's disease, Polymyositis, Dermatomyositis, Progressive systemic sclerosis (PSS), vasculitis, Sjögren's syndrome, Raynaud's phenomenon as well as a wide array of diseases, including carpal tunnel syndrome and fibromyalgia [32-35].

Considering the distribution and symmetry of B19 arthropathy, it may suggest the diagnosis of RA. About half of patients with chronic B19 arthropathy fulfill the American College of Rheumatology criteria for RA (symmetrical involvement, morning stiffness lasting more than one hour, involvement of the hand joints, and involvement of at least three joints). Joint erosion is not seen in these patients and rheumatoid nodules are not

found. The absence of joint destruction with rheumatoid nodules is important in the differential diagnosis of RA. It has been shown that viral infection is effective in the pathogenesis of RA, with the prevalence of parvovirus B19 DNA being high in patients with rheumatoid arthritis [36-38].

A 39-year-old female patient was identified as part of a large 1994 study on the suspicion that parvovirus B19 induces musculoskeletal disease. The patient had a flu-like illness with headache, myalgia, and axillary LAP lasting for two weeks, and a similar illness was found in her husband and two small children. In the patient who developed a painful, asymmetrical polyarthritis despite the recovery of other family members, laboratory outcomes indicated a new parvovirus B19 infection with high IgG and IgM levels. Two months after the onset of symptoms, the viral genome was noticed in serum by polymerase chain reaction (PCR) and continued positive for 10 months. The patient was first diagnosed with parvovirus B19 arthritis. However, because the symptoms could not be controlled with 3X50mg Flurbiprofen per day, Hydroxychloroquine 400 mg/day and Prednisone 10 mg/day were started in addition to the treatment. Hand and foot radiographs were normal at baseline, However, during the 8th month cortical erosions were seen in several small joints. Therefore, 20 mg/week Sodium aurothiomalate was started instead of Hydroxychloroquine and a gradual improvement was observed. In this study, it was concluded that the diagnosis of new parvovirus B19 infection, can be obtained with false low positive IgM results with some tests, should be made correctly. In addition, the relationship between parvovirus B19 and some forms of RA (particularly early in the process) was noted to merit further investigation [39]. Another study found evidence of a new parvovirus infection in 4-5% of 199 patients with early RA, while those with nonspecific inflammatory arthritis A new parvovirus B19 infection was noticed in 12% of 190 patients [40].

Immune electron microscopy, finding of B19 DNA and anti-B19 IgM antibodies during viremia are the main laboratory tests. The most useful modality in rheumatology clinics is anti-B19 IgM antibody serology when the patient presents with polyarthritis/polyarthralgia. Anti-B19 IgM antibody is positive 2 months later the onset of joint symptoms. It can sometimes be noticed for 6 months or longer [1]. It was conducted in a study investigating the role of parvovirus B19 in patients with arthritis of unknown origin. In this study, parvovirus B19 DNA was tried to be determined by PCR in the synovial fluid, synovial fluid cells, synovial membrane and bone marrow of 90 patients with idiopathic arthritis. Parvovirus B19 DNA was detected in the synovial membranes in 16.7% of the patients, while it was noticed in the

synovial fluid of only 1.4%. This result; developed a perspective against the background of reports reporting the presence of parvovirus B19 DNA in the synovial fluid cells and synovial fluid of patients with various arthropathy, as well as the inability to detect parvovirus B19 DNA in synovial fluid or synovial fluid cells obtained from patients with early RA diagnosis has shown [41]. There is no specific treatment or vaccine. Symptomatic treatment with NSAIDs is carried out [1].

RUBELLA

The peak incidence of Rubella transmitted by nasopharyngeal secretions is late winter-spring periods. Infection in children and adults can be asymptomatic. The classic syndrome consists of low-grade fever, malaise, rash, common cold, and prominent postauricular, posterior cervical and occipital LAP [16, 17]. Joint symptoms are common in women. The appearance of joint manifestations is one week before or after the onset of the rash. Similar to B19 arthropathy, arthralgias are more common than overt arthritis, and morning stiffness is more pronounced. Joint involvement is symmetrical or migratory and usually regresses from a few days to two weeks. PIF, MCP, wrist, ankle and knee are the most commonly involved joints. Tenosynovitis, periarthritis and carpal tunnel syndrome can be seen. In some patients, symptoms may be observed for several months or years [1,42,43].

In a study investigating an association between chronic joint disease and rubella virus, synovial fluid samples or synovial membrane biopsies from 79 patients were tested for rubella virus. 79 patients diagnosed with RA, seronegative spondyloarthropathy, juvenile chronic arthritis, osteoarthritis, infective arthropathy, gout, unexplained monoarthritis and traumatic joint injury were included in the study. In this study, rubella virus was detected in the synovial fluid of only two patients. One of the patients was a patient with generalized immunodeficiency syndrome and mycoplasma hominis arthritis. The other was a 68-year-old female patient with RA. As a result, the data obtained were insufficient to confirm the association of rubella virus with chronic inflammatory joint disease. However, it has also been reported that rubella virus can persist in the joint and reactivate when cellular immunity is suppressed. Rubella virus is not associated with chronic inflammatory joint disease. Detection of rubella virus RNA in two patients has also been attributed to decreased immunity as a result of severe immunodeficiency or in advanced age [44].

In patients with rubella arthritis, the presence of an inadequate humoral immune response to specific epitopes allows persistence of the virus.

Rubella can be detected in the synovial fluid during arthritis exacerbations and then in lymphocytes for many years, although the findings subside. Rubella virus culture was performed from synovial fluid 3-4 months after the onset of symptoms in four patients following vaccination. Because of this isolation, it was hypothesized that the virus could invade the synovium and replicate there. However, detection of sequential and circulating antibodies, with the appearance of arthritis and rash following isolation of the virus from the pharynx and blood, is consistent with an immune complex-mediated arthritis. Circulating immune complexes have been found in patients with vaccine-induced rubella arthritis [7, 44].

RUBELLA VACCINE

Three rubella vaccines were developed in 1969 (HPV 77 DE 5, HPV 77 DK 12 and Cendehill). In a short time, it was seen that all three vaccines and especially HPV 77 DK 12 cause arthritis similar to that in natural infection [7]. In a retrospective Cohort study with RA 27/3 vaccine, no relationship was found between rubella vaccine and chronic arthropathy or neurological disorder [45]. However, there are many studies reporting the relationship between rubella vaccine and arthralgia and arthritis [46-48].

Joint symptoms following rubella vaccine are similar to natural infection. However, isolated knee involvement and CTS are more common. Swelling, redness, and warmth are not common. Post-vaccine arthritis usually occurs in 2-4 weeks. Arthralgia lasts for a few days, arthritis for 1–3 weeks. However, those with knee involvement may show recurrent attacks for as long as three years [7, 49]. It is well known that hormonal changes during pregnancy exacerbate or correct autoimmune disorders. Postpartum hormonal changes (eg, increased prolactin) may affect the immune response. Prolactin is immunomodulatory and abnormalities in prolactin level have been described in disorders such as arthritis, uveitis, and thyroiditis. In addition, it has been reported that the hormonal effect in the menstrual cycle may affect the susceptibility to rubella virus vaccine-associated arthropathy [50].

Two neuropathic conditions can occur after natural infection or vaccination. In "Arm syndrome" there is brachial radiculoneuropathy, worsening at night, causing arm and hand pain, dysesthesia. "Catcher's crouch syndrome" is lumbar radiculoneuropathy and is characterized by pain in the popliteal fossa that appears in the morning. Symptoms aggravate with knee extension, and pain gradually decreases with the "catcher's crouch" position. Both syndromes, defined 1-2 months after vaccination, can be observed. Episodes may recur over a period of about 1 year but eventually resolve without se-

quelae [51, 52]. Rubella is easily cultured as a laboratory study from tissues and bodily fluids, including throat swab. Anti-IgG antibody seroconversion or Anti-Rubella IgM positivity is diagnostic for rubella infection. IgG and IgM are often present at the onset of joint symptoms. The IgM peak occurs 8–21 days after the onset of symptoms, and in most patients, this peak is not detectable after 5 weeks [1, 2]. Non-steroidal anti-inflammatories can be used to control symptoms in treatment. Some researchers state that low or moderate doses of corticosteroids are necessary to control symptoms and viremia [3, 4].

ALPHA VIRUSES

Alpha viruses are mostly seen in endemic regions of the world. O'nyong-nyong virus, Ross river virus (Australia's epidemic polyarthritis), Chikungunya virus, Barmah–Forest virus, Sindbis virus, Mayaro virus and Igbo-Ora virus are the arthritogenic viruses studied in this group [3, 6, 7].

Chikungunya virus causes epidemics in Asia, India, Indonesia, Africa and South America. It is transmitted by mosquitoes. Fever detected in chikungunya has a characteristic explosive onset, accompanied by severe arthralgia with fever. There is a maculo-papular rash, and the fever reaches 39-40 degrees. Widespread muscle pain, low back and shoulder pain are common findings. Stiffness and swelling, migratory polyarthralgia affects the wrists, small joints of the hand, feet and ankles. Large joint involvement is rare. Joint symptoms lasting up to one year may occur in 10% of patients. Destructive arthropathy has also occurred in a few patients with chronic symptoms. RF may be positive at low titer in patients with prolonged symptoms. ChikungunyaIgM antibodies can remain positive for up to six months and are helpful in diagnosis in these endemic areas. Treatment is supportive. ROM exercises reduce stiffness during an acute attack. NSAIDs can be used, when insufficient, chloroquine phosphate 250 mg/day is used [8, 53].

Clinically similar to Chikungunya fever, O'nyong–nyong virus is transmitted by mosquitoes. NSAID and ROM exercise are used in the treatment. Mosquito-transmitted Igbo-Ora virus is serologically similar to O'nyong-nyong and Chikungunya virus. Ross River virus (epidemic polyarthritis), another mosquito-borne virus, is endemic in warm and tropical areas of Australia. Sudden onset of polyarthralgia occurs after an incubation period of approximately 7-11 days. There may be a macular, papular, or maculo-papular rash. In most patients, arthralgia is severe and debilitating. The joint distribution is often wandering and asymmetrical. Involvement can be detected in the interphalangeal, metacarpophalangeal, wrist, ankle and knee joints. Big toes, elbows and shoulders may also be involved. Temporoman-

dibular, hip and axial involvement may occasionally occur. Tenosynovitis and polyarticular swelling are common, paresthesias may be present. 50% of the patients can return to their daily life activities in about 1 month. There may be residual polyarthralgia, joint symptoms may recur, and relapse episodes gradually decrease. Symptomatic treatment with aspirin or NSAIDs is used in the treatment [2, 8, 54].

Sindbis virus is common in South Africa, Russia and Finland. There is rash and arthralgia. Arthritis and arthralgia involve the small joints of the hands and feet, elbows, ankles, knees, and wrists. Cases are commonly confined to forested areas. Sometimes there may be axial skeletal involvement and tendinitis is common. The extensor tendons in the hand region and the Achille tendon are involved. Chronic arthropathy is also observed as a common finding [3, 9, 53].

HEPATITIS B VIRUS

Hepatitis B virus can cause an immune complex- mediated arthritis. It starts suddenly and is often severe. Joint involvement is typically in the form of simultaneous, symmetrical association of several joints. Arthritis can be additive or migratory. Hand joints and knees are most commonly affected, but elbows, wrists, shoulders, and other large joints may also be affected. Morning stiffness often occurs. Urticaria and arthritis, which may appear days or weeks before jaundice, may persist for several weeks, usually after jaundice. The rash and arthritis often regress after the clinical manifestation of jaundice. Arthritis is limited to the preicteric prodromal period. Recurrent polyarthralgia or polyarthritis may be observed in patients with chronic active hepatitis or chronic HBV viremia. There are publications showing a relationship between hepatitis B virus infection and autoimmune diseases such as autoimmune hepatitis, SLE, antiphospholipid syndrome, polyarteritisnodosa (PAN), multiple sclerosis, thyroid diseases and uveitis [55-57].

Presence of urticaria in the presence of polyarthritis suggests the presence of HBV infection. Asymptomatic Acute hepatitis may also occur. When arthritis occurs, bilirubin and transaminase levels are elevated. When arthritis occurs, serum HBs antigen (Ag) can also be seen at a peak level. Viral DNA, virions, polymerase and Hbe antigen can be detected in serum. AntiHBc IgM antibodies are present, indicating acute HBV infection [55, 56].

Immune complex deposition in the synovium is thought to be at the forefront in the pathogenesis of HBV arthritis. Complexes appear in the prehepatic period when HBs Ag is increased and the skin and joints are clin-

ically active. These include HBs Ag and anti-HBs, other immunoglobulins and complement components [55, 57].

Arthritis often accompanies the rash, which is commonly urticarial but may be macular, papular, or petechial. All three types of rash may coexist in the same patient. When arthritis is present in the laboratory, HBs Ag is usually detected in the blood. However, several samples may need to be tested before a positive result can be obtained. As the arthritis heals, HBs Ag usually disappears and anti-HBs becomes positive. In the period of arthritis, cryoprecipitates can be detected in the serum of some patients. These precipitates are large immune complexes containing HBs Ag, anti–HBs, IgM, A, G, and complement (C) 19, C3, C4, and C5 [7, 55-57]. Complement components can be rapidly depleted when arthritis first appears. During this time, C4 and CH50 levels were often markedly decreased. C3 level may be low or normal. Low complement levels are not found in all patients. The highest HBs Ag concentrations are associated with the lowest C19 and C4 levels [7.] There is also ample evidence for the presence of circulating immune complexes to explain the extrahepatic findings in hepatitis B infection [57].

Acute hepatitis B may present as a polyarthritic syndrome with a symmetrical pattern that mimics RA, primarily affecting many joints. One study evaluated the clinical significance of HBV in 50 patients with an early diagnosis of RA (≤12 months). All 50 patients fulfilled the RA criteria of the American College of Rheumatology (ACR). Serological markers for HBV were found in 4 of 50 patients (8%) as a result of investigations. HBs Ag of two of them was positive [58]. Joint discomfort may be the only sign of acute hepatitis B infection. Persistence of joint symptoms is rare in patients who become chronic. Arthralgias usually disappear, although the infection persists. Arthralgia may be due to virus-induced transient interferon production by the patient. Arthralgia is also a common symptom in patients treated with interferon. Wands et al. detected circulating immune complexes only in patients with acute hepatitis B complicated by arthralgia. However, they stated that immune complexes in patients with significant arthritis and other signs of serum sickness reaction were qualitatively different. It does not contain IgM, IgG or C3 or C4 [55, 59]. Early results show that the response to IFN therapy is better in patients with extrahepatic manifestations of HBV infection. This interesting observation can be confirmed by further research [59].

Polyarthritis, erythema nodosum, uveitis and reactive arthritis (HLA B27 positivity in two cases) have been reported after hepatitis B vaccination. HLA B27 positivity was also reported in another patient who developed

reactive arthritis two weeks after the second administration of recombinant hepatitis B vaccine (Engerix B) [60].

Biasi et al. reported a 41-year-old male patient who received the second dose of hepatitis vaccine three weeks after the first dose of hepatitis vaccine, although there was no complication after the first dose, and 15 days after that, pain, swelling, and limitation appeared in the knees, right shoulder, right wrist, right MCP, and right big toe. HBs Ag (-), anti-HBs: (+) and immune complexes circulating above normal were detected in the patient. Except for mild hepatomegaly and slightly increased ESR, all other laboratory tests are normal. In line with these data, the patient was diagnosed with reactive arthritis, 150 mg/day indomethacin was started, and a gradual improvement was observed within four months. This case illustrates an unusual reaction to hepatitis B vaccine in a healthy individual. Natural HBV infection is known to induce arthritis. It is reasonable to think that in genetically susceptible individuals, viral antigens made may trigger a reactive arthritis [60].

HEPATITIS C VIRUS

Joint involvement may be the most common extrahepatic manifestation of HCV infection. HCV occurs in two different clinical manifestations. The first is symmetrical polyarthritis and the second is intermittent monoarthritis. Symmetrical polyarthritis occurring in acute hepatitis C infection is an acute onset polyarthritis in a rheumatoid distribution that includes the small joints of the hand, shoulders, wrists, hips and knees. Differentiation of symmetrical polyarthritis from RA is difficult. The presence of anti-CCP antibodies is helpful in the differential diagnosis of hepatitis C arthritis from RA. Coexistence of type II cryoglobulinemia and HCV is common. This triad of "arthritis–cryoglobulinemia–palpable purpura" is in the form of essential mixed cryoglobulinemia [1, 61, 62].

Despite strong antibody response to viral epitopes, HCV infection may persist. The high mutation rate in the envelope protein is responsible for the emergence of mutants that survive neutralization and the development of similar species. Interferon-alpha (IFN- α) is an effective treatment for hepatitis C hepatitis and cryoglobulinemia associated with HCV. Hepatitis C arthritis is non-erosive and does not leave deformity. It occurs in 2-20% of patients [1, 61].

Three patients with polyarthritis who subsequently were found to have positive HCV serology were reported in one study. The first case was hospitalized for rehabilitation iv. A 37-year-old male patient with drug use. There is a slight effusion on the left knee and ankle. No heat increase or erythema.

HCV (+) hepatitis profile was detected. The second case is a 44-year-old male patient with intermittent arthritis and arthralgia in his hands and wrists for 10 years. He was diagnosed with hepatitis 10 years ago, but he does not know the type. She has a skin lesion, diagnosed as porphyria cutenea tarda. Liver biopsy: It was found to be compatible with HCV. Serology confirmed HCV infection. He was given ibuprofen for his arthritis and improvement was observed. The third case is a 31-year-old male patient. 5U during surgery five years ago. Blood has been given. He has had severe migratory arthritis for three weeks. Morning stiffness lasts for two hours. This patient was started on treatment for an inflammatory arthritis (possibly atypical RA). Since there was no response to NSAIDs and analgesics, methotrexate 10 mg/week was started. Symptoms improved dramatically. Liver function tests continued to be elevated and HCV was positive. Repeated tests also showed persistence of HCV. Liver biopsy was found to be compatible with HCV. Methotrexate was discontinued after five months. After discontinuation of methotrexate, the patient's arthritic symptoms worsened rapidly. Methotrexate treatment was rearranged, and a clear and rapid recovery was observed again. Repeated X-rays did not show any bone abnormalities or osteopenia. Although this patient has RF (+), the presentation is atypical RA [63]. Mc. Carty and Ormiste differentiated between physical findings in RA and HBV-associated arthritis. Accordingly, in hepatitis B arthritis, joint tenderness is localized to a single area around the joint, erythema and temperature increase are rare, and there is usually no synovial thickening. Fever, anemia, high ESR, joint deformity and destruction are features of RA and are rare in hepatitis-associated arthritis. RF positivity is also seen in the course of HBV infection. Interestingly, there have been three reports of pseudo (+) HCV serology in patients with RA. However, when there is histological evidence with liver biopsy, the opposite should be considered. The third patient's response to methotrexate is interesting. It has not been determined whether methotrexate would also be beneficial in other patients with HCV arthritis. This drug should be used with caution in patients with liver disease [63, 64].

Other extrahepatic conditions associated with chronic hepatitis C infection are fibromyalgia, systemic lupus erythematosus, antiphospholipid syndrome, and osteosclerosis [63-65].

HERPES VIRUSES

Varicella Zoster Virus arthritis is a rare complication in children and is most commonly seen as monoarthritis. In infectious VZV, the causative

agent was isolated from synovial fluid, and PCR showed virus DNA in the synovial fluid of a patient with suspected varicella arthritis [66]. PCR is a sensitive method that shows virus DNA even though cultures are negative. Varicella arthritis usually heals within 1 week. Septic arthritis, which is thought to be due to staphylococci and streptococci originating from the skin, may also develop in varicella arthritis. For differential diagnosis, synovial fluid analysis should be performed [67, 68]. The most frequently involved joints are the knee, followed by the ankle, shoulder and hip bones. Varicella arthritis, unlike mumps or rubella arthritis, is not migratory. The severity of skin lesions in varicella is not correlated with the number of joints involved. The variability of varicella arthritis suggests that different pathological mechanisms are involved. The style of arthritis is similar to a reactive arthritis. Pathogenesis may be multifactorial [69]. Another study reported an adult patient with recurrent synovitis and an episode triggered by varicella. T cell response to bacterial agents (camphylobacter) was detected in the patient who had previously had swelling and pain in the left knee. The patient complained of pain and swelling in the left knee after the chickenpox episode. Significant T-cell response to VZV was obtained eight weeks after the chickenpox episode. However, it has not been clarified whether the arthritis is caused directly by VZV itself or by the reactivation of sensitivity to bacterial antigens by finding a way of viral infection. Although the exact mechanism is not known, this shows that different viral and bacterial stimuli can trigger synovitis in the same joint but at different times [66].

Arthritis with herpes simplex type-1 and Cytomegalovirus (CMV) is rare. Severe CMV polyarthritis has been reported in a few immunocompromised patients undergoing bone marrow transplantation. HSV-1 arthritis begins 3-4 days after the typical skin lesion and monoarthritis usually lasts for two weeks. The erythrocyte sedimentation rate may be over 100 mm/hr [65, 67].

Arthritis is rare, although approximately 2% of patients with Infectious Mononucleosis caused by Epstein-Barr virus have arthralgia. However, several case reports indicate that this complication is higher than expected. In the serological examination of nine patients with acute-onset seronegative polyarthritis, four were found to have acute or chronic EBV infection . The pathogenesis is unknown, it is assumed that viral replication and precipitation of immune complexes occur within the synovium . It has been reported that anti-EBV antibody response is associated with RA as one of the chronic antibody responses [7, 70-72].

In a study dated 1999, it was stated that although arthralgia may occur with EBV infection, inflammatory synovitis was still detected in four pa-

tients and a case report is made. This 15-year-old case is a previously healthy female patient. Acute pharyngitis, cervical LAP and malaise developed. In physical examination; Erythematous pharynx, cervical LAP and palpable spleen tip are present. Mono-spot test: (+), pharyngitis and LAP regress without treatment. In the physical examination two weeks later; There is an enlarged hot right knee, a tight joint effusion, and ROM limitation. No LAP and no splenomegaly. Synovial fluid BK: 6140 (2% neutrophils, 62% lymphocytes, 35% monocytes), cultures: (-). Viral capsid antigen IgG antibody titer in EBV serology is 1/640, viral capsid antigen IgM antibody titer is 1/40. 40 mg of triamcinolone was administered to the knee joint, arthritis and symptoms regressed in a few days, and the patient remained asymptomatic. The resulting arthritis is more reactive than a direct replicative viral infection . Steroid injection is an attractive option in the treatment of this type of reactive arthritis [70].

RETROVIRUS

HTLV-1: Human T-lymphotropic virus-1 virus is endemic in Japan. HTLV-1 has been observed with oligoarthritis and nodular rash. Atypical synovial cells with lobulated nuclei and T cell synovial infiltrates indicate direct involvement of synovial tissue through the leukemic process. Arthritis in the form of oligoarthritis of large and medium-sized joints may be detected [73].

The human immunodeficiency virus (HIV): The most common articular syndromes observed in HIV infection; HIV-associated arthropathy, seronegativespondyloarthropathies (SPA), reactive arthritis, psoriatic arthritis (PsA) are undifferentiated SPA, RA and painful articular syndrome (AAS). In addition, myositis, polymyositis, non-inflammatory myopathies, and drug-induced disease may be Sjogren's-like disease (characterized by diffuse lymphocytic infiltrates) [1, 74].

Reiter's syndrome (RS): This sexually transmitted rheumatic disease, which is more common in men; it can start with any of the triad of "arthritis, urethritis, and conjunctivitis". Reiter's Syndrome can be observed as an aseptic peripheral arthritis in people with HIV infection. Most patients have extra-articular symptoms reflecting Reiter's Syndrome (urethritis, ocular inflammation and skin lesions). In these patients, articular disease primarily affects the knees, ankles, and feet. Hand, wrist and upper extremity involvement is observed in a minority of patients. Enthesopathy may also be seen in areas compatible with the Achilles tendon, plantar fascia, anterior and posterior tibial tendons. This disease is unrelated to radiographic changes and can be easily controlled with NSAIDs. However, there may be rare cases with

radiographic periostitis and erosions and very resistant to anti-inflammatory therapy. While HLA B27 is found to be negative in African HIV-positive reactive arthritis, 80% of Caucasian patients have HLAB27 positivity [1, 74].

Psoriatic arthritis: When HIV infection and psoriatic arthritis coexist, a spectrum of papulosquamous dermopathy is observed. These changes range from the mild end of seborrheic dermatitis to the severe end of prominent psoriasis vulgaris and even pustular psoriasis. Arthritis and enthesopathy are similar to that described in Reiter's Syndrome, which can occur at the same time as psoriasis. Psoriasis-based arthritis is more common in HIV-infected patients than in non-HIV-infected patients. Because keratoderma blennorrhagicum and pustular psoriasis are often indistinguishable, it is difficult to distinguish incomplete Reiter's Syndrome from psoriatic arthritis. Recent studies have emphasized that psoriasis, psoriatic arthritis, and Reiter's Syndrome are sequential and chronic diseases in HIV-infected individuals. Studies in HIV-positive patients with psoriasis have shown that these patients have more severe and persistent skin lesions. Similarly, joint findings are more severe and erosive arthropathy resistant to conventional treatment occurs. Joint involvement can be observed in the form of asymmetric oligo or polyarthritis localized to the lower extremities [1,75,76].

HIV-associated arthritis: In many prospective series examining articular disease in HIV infection, the most common condition other than arthralgia was found to be seronegative arthritis. A distinctive syndrome of acute oligoarthritis, which commonly affects the knees and ankles and can last from hours to several days, has been described as the painful articular syndrome (PAS) [1, 77].

Acute symmetrical polyarthritis has been reported. The clinical spectrum can be acute or subacute, ranging from minimal swelling and tenderness to swan neck deformity. The relationship between HIV infection and RA is a matter of considerable debate [1, 74]. Some studies report that RA disease activity decreases after HIV develops in patients with previously diagnosed RA and argue that HIV improves RA symptoms [78-79].

Undifferentiated seronegativespondyloarthropathies: Achilles tendinitis, dactylitis, low back pain, plantar fasciitis, ankle pain, shoulder pain. Uveitis and axial involvement are rare.

Septic Arthritis: iv. Bacterial infection of the joints has occasionally been reported in HIV-infected patients without risk factors for septic arthritis, such as drug use. These infections are often due to staphylococcus aureus and streptococcus pneumoniae. Opportunistic infections of the joints have

also been rarely reported in isolated cases. These are sporothrix schenckii, cryptococcus neoformans, candida albicans, histoplasma capsulatum and mycobacterium avium-intracellular [1].

Arthritis Treatment in HIV-Positive Patients: Non-steroidal anti-inflammatories (NSAIDs) are the first choice in HIV-associated arthritis. Disease-modifying drugs are rarely required, as they are typically of a self-limiting nature. Undifferentiated SPA and all other forms of SPA. It improves with antiretroviral therapy [81]. Interestingly, the antiretroviral efficacy of both indomethacin and hydroxychloroquine has been demonstrated in a small case series [82,83]. The use of leflunomide 20 mg/day has been found to reduce HIV replication [84]. Azathioprine, gold preparations have been reported to be effective in HIV-positive patients with PsA [85]. Biological agents can be used in HIV-positive patients with an interestingly good safety profile [86].

OTHER VIRUSES

In adults with mumps, synovitis may occasionally occur in the small or large joints[1,6]. In one study, a case of monoarthritis due to mumps component was reported after mumps and measles immunization. The case was a 19-month-old boy who developed a transient rash, fever, and enlarged parotid glands eight days after measles and mumps vaccination. In five days, her current symptoms regress. After 15 days, he has a fever and begins to use his left leg. In physical examination; The left knee was found to be hot, tender and swollen. ROM decreased, BK: 15800, Erythrocyte sedimentation rate: 50.5 cc in synovial fluid aspiration. Turbid liquid was obtained, BK: 4300 and cultures were determined as sterile. The virus could not be isolated from the nasopharynx and throat. One month later, mumps antibodies measured by the complement fixation method were found to be IgG: 1/69. Five days to the patient iv. Cefuroxime was given oral cephalexin for 21 days. Symptoms regressed within 24 hours and remained asymptomatic for three years. Mumps arthritis is a form of monoarthritis or polyarthritis, primarily involving large joints (knees, ankles, hips). There is an interval of 1-3 weeks between parotitis and the onset of arthritis. It is self-limiting and lasts for a few days to a few weeks and does not cause permanent damage to the joint [87].

Mumps arthritis was diagnosed in a patient who was immunized against measles and mumps for three reasons: 1. The temporal relationship between vaccination and the onset of parotitis, 2. Serological data, 3. Not considering other causes of arthritis. It is unlikely that the arthritis is due to the

measles component. Because arthritis after measles infection or vaccination has not been defined [88].

Adenovirus and Coxsackievirus A9, B2, B3, B4, and B6 may be associated with recurrent episodes of polyarthritis, pleuritis, myalgia, rash, pharyngitis, and myocarditis. A few cases of polyarthritis, fever and myalgia have been reported with ECHO virus 9 infection [1-3, 6-9].

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