Viral Arthritis

STANLEY J. NAIDES

The response may generate immune complexes that are deposited locally at the site of viral infection or systemically in synovium. Alternatively, cells may survive, but their behavior may be altered by the expression of viral genes. Transactivation of cellular genes by viral gene products may induce the cell cycle or cytokines that elicit or perpetuate an immune response targeting host cells. Molecular mimicry of host autoantigens by viral proteins may break immune tolerance. Viral components may elicit “danger signals” that trigger an immune response.12

PARVOVIRUS B19

Human parvovirus B19 is a member of the family Paroviridae, subfamily Parovirinidae, genus Erythrovirus. It consists of the small, single-stranded DNA viruses that autonomously replicate in erythroid precursors (hence the genus name). B19 has no envelope and is approximately 23 nm in diameter. Productive infection occurs in erythroid precursors; infection of nonerythroid tissues occurs but is restricted, which means that if assembly of virions occurs, it is inefficient, or that nonstructural but not capsid structural viral genes are expressed, preventing virion assembly. Parvoviruses are species specific and are not known to readily cross species barriers. The common canine parvovirus does not infect humans.

Epidemiology

B19 infection is common and occurs worldwide. B19 typically is transmitted by respiratory secretions but may also be transmitted via pooled blood products. Outbreaks commonly occur in late winter and spring, when close contact is most common, although epidemics may also occur in summer and fall. Most B19 infections, especially in children, remain asymptomatic or are diagnosed as nonspecific viral illnesses. Outbreaks tend to occur in 3- to 5-year cycles, representing the time required for a new cohort of susceptible children to enter school. Up to 60% of adults have serologic evidence of past B19 infection.14 Susceptible adults in occupations with multiple exposures to children, such as schoolteachers and pediatric nurses, are at greatest risk (up to 50%) of acquiring infection during outbreaks.15 Sporadic cases do occur during nonepidemic periods. The diagnosis should be entertained even in the absence of surveillance data suggesting an outbreak.

Pathogenesis

The onset of joint symptoms and rash is associated temporally with the appearance of serum anti-B19

Viruses are candidate causative agents for various rheumatic diseases in part because arthralgia and arthritis are prominent features of certain viral infections. Understanding how viruses cause arthritis and the nature of virus–host cell interactions may suggest how viruses precipitate, establish, or maintain chronic inflammatory arthritis such as rheumatoid arthritis.

Viral effects in a given host may depend on host factors such as age, gender, genetic background, infection history, and immune response. The ability of a given virus to infect a host may also depend on the viral mode of host entry, tissue tropism, replication strategy, cytopathologic effects, ability to establish persistent infection, viral expression of host-like antigens, and ability to alter host antigens. Viral modification of the regulation of cellular gene expression may contribute to autoimmunity. Infected cells may die by classic cell necrosis, programmed cell death (apoptosis), or autophagy. Initiation of an immune response to virally encoded antigens on the cell surface may target that cell for destruction and alter cell-cell interactions. The antibody response may generate immune complexes that are deposited locally at the site of viral infection or systemically in synovium. Alternatively, cells may survive, but their behavior may be altered by the expression of viral genes. Transactivation of cellular genes by viral gene products may induce the cell cycle or cytokines that elicit or perpetuate an immune response targeting host cells. Molecular mimicry of host autoantigens by viral proteins may break immune tolerance. Viral components may elicit “danger signals” that trigger an immune response.12

**KEY POINTS**

- Acute-onset, symmetric polyarthritis can be caused by viral infection, especially when accompanied by rash.
- Always take exposure, travel, occupation, and vaccination histories.
- Parvovirus B19 is the most common viral arthritis in the United States.
- In adults with parvovirus B19 infection, rash may be subtle or absent.
- Rubella arthritis occurs in young adults. Rubella vaccination has reduced the overall incidence of rubella infection but has shifted the peak age to young adults.
- Arthralgia, arthritis, or neuropathic pain may occur after rubella vaccination; these conditions are usually self-limited in duration.
- Alphaviruses are mosquito-borne causes of arthritis and rash. Outbreaks occur in endemic areas associated with rising mosquito populations and should be considered in travelers entering the United States.
- Hepatitis B virus infection presents as an arthritis-urticaria syndrome.
- Hepatitis C virus infection causes cryoglobulinemia and vasculitis. Cryoglobulinemic vasculitis often presents as palpable purpura of the lower legs.
- The history of risk behaviors associated with hepatitis C virus infection may be remote.
immunoglobulin (Ig)M antibody, suggesting a role for circulating immune complexes during the acute phase of the illness. Although little evidence of circulating virus has been found in patients who have chronic joint symptoms, B19 DNA may be found in the bone marrow and synovium of patients with chronic B19 arthropathy. Persistence in chronic B19 arthropathy may be facilitated by failure to develop IgG antibodies to the N-terminal region of the minor capsid protein VP1, known to encode neutralizing epitopes. The presence of antibody to the B19 nonstructural protein NS1 in some cases of chronic B19 arthropathy probably reflects the immune response to NS1 on the surface of B19 virions or NS1 spilled during cell death. NS1 protein itself, however, may play a pathogenic role in perpetuating chronic B19 arthropathy through its interaction with cellular genes. NS1 protein upregulates in vitro transcription from the interleukin (IL)-6 promoter and from human immunodeficiency virus (HIV) long terminal repeats in the presence of tat and an intact tat element. A high prevalence of B19 DNA and proteins in synovium from rheumatoid arthritis patients was reported in association with enhanced synovial production of IL-6 and tumor necrosis factor. These findings remain controversial. B19 may induce apoptosis through NS1, which is known to be toxic to cells. Production of NS1 in nonpermissive synoviocytes could theoretically induce autoimmunity by disrupting normal patterns of cell interactions and intercellular regulation.

**Diagnosis**

**Clinical Features**

The incubation period from B19 infection to symptom onset is 7 to 18 days. B19 causes transient aplastic crisis in the setting of chronic hemolytic anemia. In otherwise healthy children, B19 causes erythema infectiosum, or fifth disease, characterized by bright red “slapped cheeks” and a macular or maculopapular eruption on the torso and extremities. Up to 70% of infected children may be asymptomatic; others may have mild flu-like symptoms, including fever, headache, sore throat, cough, anorexia, vomiting, diarrhea, and arthralgia. In adults, the rash tends to be subtler, and the slapped-cheek rash is usually absent. Uncommon dermatologic manifestations include vesicular or hemorrhagic vesiculopapular eruptions, purpura with or without thrombocytopenia, Henoch-Schönlein purpura, and a “socks and gloves” acral erythema. B19 infection may be associated with paresthesias in the fingers and, rarely, with numbness of the toes. Progressive arm weakness has been associated with mild nerve conduction slowing and decreased motor and sensory potential amplitudes. B19 may cross the placenta to infect the fetus, which may develop hydrops fetalis on the basis of B19-induced anemia or viral cardiomyopathy. Less commonly, B19 may cause pancytopenia, isolated anemia, thrombocytopenia, leukopenia, myocarditis, neuropathy, or hepatitis. Reports suggest that B19 may be associated with vasculitis, including giant cell arteritis.

Patients with congenital or acquired immunodeficiencies, including prior chemotherapy or acquired immunodeficiency syndrome (AIDS) due to HIV infection, may develop persistent B19 infection with chronic or recurrent anemia, thrombocytopenia, or leukopenia. B19 infection is the leading cause of pure red cell aplasia in patients with AIDS.

In a study of an erythema infectiosum outbreak in Port Angeles, Washington, in which subjects were identified on the basis of rash, the incidence of arthralgia and joint swelling increased with age (Table 114-1). In adults, a severe flu-like illness consisting of fever, chills, malaise, and myalgias may precede or accompany sudden-onset, moderately severe, symmetric polyarthritis in a rheumatoid-like distribution. The arthritis is characterized by prominent involvement of the finger proximal interphalangeal, metacarpophalangeal, wrist, knee, and ankle joints. Within 24 to 48 hours of onset, all affected joints become involved. Axial skeleton involvement is uncommon. Joint symptoms are usually self-limited.

After the initial infection, objective joint swelling, heat, and erythema, when present, tend to resolve over several weeks. A minority of patients have prolonged symptoms that fall into one of two patterns. Approximately two-thirds have continuous morning stiffness and arthralgias with intermittent flares. The remaining patients are symptom free between flares. Chronic B19 arthropathy may last months to years. Pain remains a prominent feature during flares; patients commonly report morning stiffness. Approximately 12% of patients presenting with “early synovitis” have B19 infection; most are women.

**Laboratory Tests**

Viremia lasts 5 to 6 days and is associated with an absence of reticulocytosis and, in otherwise normal individuals, a minimal decrease in the concentrations of hemoglobin, neutrophils, and lymphocytes. Flu-like symptoms may occur during viremia. An IgM antibody response follows the initial viremia in 4 to 6 days and is associated with clearing of viremia and cessation of nasal shedding of virus.

The antibody response is associated with the second phase of clinical illness, characterized by rash and joint symptoms. Onset of the anti-B19 IgG antibody response occurs almost concurrently with the IgM response. The two clinical phases of illness often overlap. Low to moderate titers of rheumatoid factor and anti-DNA, antilymphocyte, antinuclear, and antiphospholipid antibodies may be present initially.

During viremia, immune electron microscopy may detect virions in serum. However, this method is not readily available to clinicians. B19 DNA may be detected during viremia. However, because adult patients usually present

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**Table 114-1  Prevalence of Joint Symptoms in Fifth Disease by Age: Port Angeles, Washington, 1961-1962**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>0-9 yr</th>
<th>10-19 yr</th>
<th>&gt;20 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>5.1</td>
<td>11.5</td>
<td>77.2</td>
</tr>
<tr>
<td>Swelling</td>
<td>2.8</td>
<td>5.3</td>
<td>59.6</td>
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</table>

after the onset of joint symptoms, the most useful diagnostic test is anti-B19 IgM serology. Radioimmunoassays and enzyme-linked immunosorbent assays have been used to detect B19 antigen and specific antibody to B19 capsid and envelope glycoproteins. The anti-B19 IgM antibody response is usually positive for 2 months after the acute illness and may wane shortly thereafter. In some patients, anti-B19 IgM may be detected for 6 months or longer. A positive anti-B19 IgG antibody test in the absence of anti-B19 IgM usually is not diagnostically helpful because of the high seroprevalence of anti-B19 IgG in the adult population. Reports of B19 DNA in normal synovium suggest that testing for B19 DNA in these tissues is of little clinical utility in the absence of anti-B19 IgM.  

Differential Diagnosis

Many patients with B19 arthropathy meet the American Rheumatoid Arthritis criteria for a diagnosis of rheumatoid arthritis: morning stiffness lasting longer than an hour; symmetric involvement; involvement of at least three joints; and involvement of the finger proximal interphalangeal, metacarpophalangeal, and wrist joints. Rheumatoid factor may be present at low to moderate titers. Absence of both rheumatoid nodules and joint destruction differentiate B19 arthropathy from classic, erosive rheumatoid arthritis.

Occasionally, B19 infection may present with features of systemic lupus erythematosus (SLE). Whether this represents a clinical mimic or indicates that B19 plays a role in initiating or precipitating SLE in these patients remains to be determined.  

Rubella in adults may present with rash and symmetric polyarthralgia or polyarthritis that is clinically indistinguishable from B19 infection. A history of prenatal rubella testing, prior rubella vaccination, or rubella exposure may aid the clinician in choosing the appropriate diagnostic serologies.

Treatment and Outcome

No specific treatment or vaccine has been identified for B19 infection. Therefore, treatment is symptomatic and consists of nonsteroidal anti-inflammatory drugs. Intravenous immunoglobulin has been successful in the treatment of bone marrow suppression and B19 persistence in immunocompromised patients, but initial studies suggest that this is not applicable to patients with chronic arthropathy. Long-term prognosis is good. Although subjective arthralgias and morning stiffness may be prolonged, joint destruction is not a feature of chronic B19 arthropathy. The role of B19 as a cofactor in the development of classic erosive rheumatoid arthritis has not been confirmed.

TOGAVIRUSES

The family Togaviridae includes the Rubivirus and Alphavirus genera.

Rubella Virus

Rubella virus is the sole member of the genus Rubivirus. It consists of enveloped, single-stranded RNA viruses. The rubella virion is spherical and measures 50 to 70 nm in diameter, with a 30-nm dense core. Envelope glycoproteins form 5- to 6-nm spike-like projections that contain hemagglutination activity.

Epidemiology

Transmission is by nasopharyngeal secretions, with a peak incidence in late winter and spring. Vaccination has reduced the incidence of rubella outbreaks and has shifted the demographic profile from children to college students and adults. The incubation period from infection to rash is 14 to 21 days. Viremia precedes rash by 6 to 7 days, peaks just before the onset of rash, and clears within 48 hours after the onset of rash. Nasopharyngeal shedding of virus is detectable from 7 days before the appearance of rash until 14 days afterward, but it is maximal from just before the rash until 5 to 6 days later.

Pathogenesis

Rubella virus can persistently infect synoviocytes and chondrocytes in vitro. An inadequate humoral immune response to specific rubella envelope glycoprotein epitopes may allow rubella virus to persistently infect synovium and lymphocytes in patients with chronic rubella arthritis. The onset of rash and arthritis is concurrent with antibody production, suggesting a role for antibody or immune complexes. Concentrations of rubella antibody are higher in synovial fluid than in serum. Synovial lymphocytes from infected individuals spontaneously secrete rubella antibody in vitro, suggesting that an immune response to rubella infection occurs in the joint.

Diagnosis

Clinical Features. Asymptomatic infection occurs in children and adults. Low-grade fever, malaise, coryza, and prominent lymphadenopathy involving posterior cervical, postauricular, and occipital nodes may precede rash by 5 days. A morbilliform rash may initially appear on the face and then spread to the torso, upper extremities, and lower extremities over 2 to 3 days. The facial rash may coalesce and clear as the extremities become involved. In some cases, the rash is only a transient blush.

Joint symptoms commonly occur in women beginning 1 week before or 1 week after the appearance of the rash. Symmetric or migratory arthralgias are more common than synovitis. Morning stiffness is prominent. Joint symptoms usually resolve over a few days to 2 weeks. Proximal interphalangeal, metacarpophalangeal, wrist, elbow, ankle, and knee joints are most frequently affected. Periarthritis, tenosynovitis, and carpal tunnel syndrome may be seen. In some patients, symptoms may persist for months to years.

Live attenuated rubella vaccines have caused a high frequency of postvaccination myalgia, arthralgia, arthritis, and paresthesia—symptoms similar to those seen in natural infection—beginning 2 weeks after inoculation and lasting less than a week. However, in some patients, symptoms may persist for longer than a year. RA27/3, the vaccine strain in current use, may cause postvaccination joint symptoms in 15% or more of recipients.
Two rheumatologic syndromes may complicate natural infection or vaccination in children. In the chicken's crouch syndrome, a lumbar radiculoneuropathy causes plopilateral fossa pain on arising in the morning. Exacerbation of the pain by knee extension encourages the assumption of a baseball catcher's crouch position. The pain gradually subsides through the day but recurs the next morning. In the arm syndrome, brachial neuropathy causes arm and hand pain and dysesthesias that are worse at night. Both syndromes may occur beginning 1 to 2 months after infection or vaccination, with the initial episode lasting up to 2 months. Episodes recur for up to 1 year but eventually resolve without long-term sequelae.

Laboratory Tests. Although rubella may be cultured from tissues and body fluids, including throat swabs, detecting antirubella IgM antibody usually establishes the diagnosis of acute rubella infection. Diagnosis by anti-IgG antibody seroconversion requires paired acute and convalescent sera. IgM and IgG are usually present at the onset of joint symptoms. IgM antibody levels peak 8 to 21 days after symptom onset and wane by 5 weeks. Antirubella IgG rises rapidly over a period of 1 to 3 weeks and is long lived. A single positive IgG serum sample or a set of untitered IgG-positive screens documents only immunity.

Differential Diagnosis. Rubella arthritis needs to be differentiated from other viral arthritides and from inflammatory arthritides, including rheumatoid arthritis. It may be confused with parvovirus B19 infection.

Treatment and Outcome
Nonsteroidal anti-inflammatory drugs are useful to control symptoms. Some investigators have suggested the use of low to moderate doses of steroids to control symptoms and viremia. Long-term prognosis is good.

Alphaviruses
Members of the genus Alphavirus are enveloped, single-stranded RNA viruses transmitted by mosquitoes. Several cause acute febrile arthropathy, and their names reflect local appreciation of their clinical impact. For example, chikungunya means "that which twists or bends up" (Tanzania). The related o’nyong-nyong virus means "joint breaker" in the Acholi (Uganda) dialect. Igbo-ora is "the disease that breaks your wings."

Epidemiology
Chikungunya, o’nyong-nyong, and igbo-ora viruses form a serologically related group. Chikungunya virus was isolated during an epidemic of febrile arthritis in Tanzania between 1952 and 1953. Similar epidemics probably occurred in Africa, Asia, India, Indonesia, and possibly the southern United States as early as 1779. Mosquitoes responsible for transmission to humans define its geographic distribution (Table 114-2). A feared consequence of global warming is spread of the geographic range of infected mosquitoes.

Chikungunya fever occurs endemically and in epidemics. Outbreaks have been described in the Indian Ocean islands, Malaysia, and Hong Kong. An outbreak occurred in Italy in 2007. A large-scale outbreak of the serologically related o’nyong-nyong virus occurred in the Acholi province of northwestern Uganda in February 1959; this outbreak spread through Uganda and the surrounding region at a rate of 2 to 3 kilometers daily, affecting more than 2 million people within 2 years. After the initial o’nyong-nyong epidemic, clinical disease was not detected again until it re-emerged in the Acholi region in 1996. Despite the absence of outbreaks in the intervening years, serologic surveys have demonstrated that o’nyong-nyong virus is endemic.

Weber's line is a hypothetical demarcation separating the Australian and Asiatic geographic zones. Antibodies to chikungunya virus are found west of Weber's line is "the disease that twists or bends up" (Tanzania). The related o’nyong-nyong virus means "joint breaker" in the Acholi (Uganda) dialect. Igbo-ora is "the disease that breaks your wings."

<table>
<thead>
<tr>
<th>Virus</th>
<th>Mosquito</th>
<th>Reservoir</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chikungunya virus</td>
<td>Aedes species</td>
<td>Baboons, monkeys,</td>
<td>Africa, Asia</td>
</tr>
<tr>
<td></td>
<td>Mansonia africana</td>
<td>Scaphilus bat species</td>
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<td>O’nyong-nyong virus</td>
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</tr>
<tr>
<td></td>
<td>Anopheles gambiae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Igbo-ora virus</td>
<td>Anopheles funestus</td>
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<td></td>
<td>Anopheles gambiae</td>
<td>domestic animals</td>
<td>Papua New Guinea,</td>
</tr>
<tr>
<td>Ross River virus</td>
<td>Aedes vigilax</td>
<td>Culex annulirostris</td>
<td>Pacific Islands</td>
</tr>
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<td></td>
<td>Aedes camptorhynchus</td>
<td>Mansonia uniformis</td>
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<td></td>
<td>Culex annulirostris</td>
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<td>Aedes species</td>
<td>Australia</td>
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<td></td>
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<td></td>
<td>Culex species</td>
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<td>Culex species</td>
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<td>Haemagogus janthinomys</td>
<td>Marmosets</td>
<td>Bolivia, Brazil, Peru</td>
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</table>

Table 114-2  Mosquito Vectors and Reservoirs of Alphaviruses
temperate regions annually. Most cases occur in Queensland and New South Wales territories, where high rainfall and subsequent increases in mosquito populations usually precede epidemic periods. Infection rates in Australia range from 0.2% to 3.5% per year. Male and female infection rates are similar, but a female predominance has been noted in presenting cases. Most infected adults are symptomatic; the case rate for children is lower. Barmah Forest virus, another alphavirus with an increasing incidence in Australia, may manifest in a fashion similar to Ross River virus.31,56

Individuals involved in outdoor activities or occupations in forested areas in Sweden, Finland, and the neighboring Karelian isthmus of Russia are at greatest risk for infection with Sindbis virus; in those regions, it is known as Okelbo disease, Pogosta disease, and Karelian fever, respectively. Birds are the intermediate host.37 It has also been reported in central Africa, Zimbabwe, South Africa, and Australia in sporadic cases or small outbreaks.35

Mayaro virus, first recognized in Trinidad in 1954, is endemic in the tropical rain forests of Bolivia, Brazil, and Peru. Cases have been imported into the United States in individuals traveling from endemic areas.58

Diagnosis

Clinical Features. Chikungunya fever presents with an explosive onset of high fever and severe arthralgia after a 1- to 12-day incubation period. The fever lasts 1 to 7 days. Typically, a macular or maculopapular, sometimes pruritic, rash on the torso, extremities, and occasionally the face, palms, and soles occurs on day 2 to 5 of illness as the patient defervesces. The rash may last 1 to 5 days and may recur with fever. Isolated petechiae and mucosal bleeding may occur. In some patients, involved skin desquamates.59,60 Chemosis is prominent. Headache, photophobia, retro-orbital pain, pharyngitis, anorexia, nausea, vomiting, and abdominal pain may be present. Diffuse myalgia and back and shoulder pain are common. Migratory polyarthralgia, stiffness, and swelling affect predominantly the small joints of the hands, wrists, feet, and ankles. Large joints are less severely affected. Previously injured joints may be disproportionately affected. Large effusions are uncommon. Symptoms in children tend to be milder. Low-titer rheumatoid factor may be found in those with long-standing symptoms.

O’nyong-nyong fever is clinically similar to chikungunya fever.61,62 In 1984, igbo-ora caused an epidemic of fever, myalgias, arthralgias, and rash in four Ivory Coast villages. Sequencing of isolates from the 1996 outbreak of o’nyong-nyong fever suggested that igbo-ora virus is a variant of o’nyong-nyong virus.63

Ross River virus polyarthralgia is severe, incapacitating, and often migratory and asymmetric.64 Symptoms follow a 7- to 11-day incubation period. Finger interphalangeal and metacarpophalangeal joints, wrists, knees, ankles, shoulders, elbows, and toes are often involved. Polycarticular swelling and tenosynovitis are common. Arthralgias are worse in the morning and after inactivity. Rash is macular, papular, or maculopapular and may be pruritic. Vesicles, papules, or petechiae are typically seen on the trunk and extremities. The palms, soles, and face may be involved. Rash typically appears 1 to 2 days before joint symptoms, but it may occur anywhere from 11 days before to 15 days after the onset of arthralgias, and it resolves by fading to a brownish discoloration or by desquamation. Half of patients have no fever, and those who do may have only modest fever lasting 1 to 3 days. Nausea, headache, and myalgia are common. Respiratory symptoms, mild photophobia, and lymphadenopathy may occur. Up to a third of patients have paresthesias and palm or sole pain. Carpal tunnel syndrome may be seen. Arthritis is less common and less prominent in Barmah Forest virus infection than in Ross River virus infection, but the rash is more common and florid.64,65

Rash and arthralgia are the presenting symptoms in Sindbis virus infection, although one may precede the other by a few days. Constitutional symptoms are usually mild and include low-grade fever, headache, fatigue, malaise, nausea, vomiting, pharyngitis, and paresthesias. A macular rash typically begins on the torso and then spreads to arms and legs, palms, soles, and occasionally the head. Macules evolve to form papules that tend to vesiculate. Vesiculation is prominent on pressure points, including the palms and soles. As the rash fades, a brownish discoloration is left. Vesicles on the palms and soles may become hemorrhagic. The rash may recur during convalescence.66

A Mayaro virus outbreak in Belterra, Brazil, in 1988 was characterized by sudden onset of fever, headache, dizziness, chills, and arthralgias in the wrists, fingers, ankles, and toes. The clinical attack rate was 80%. Joint swelling, unilateral inguinal lymphadenopathy, and leukopenia may be present. A maculopapular rash on the trunk and extremities lasts about 3 days.67

Laboratory Tests. The diagnosis of alphavirus infection requires laboratory confirmation. Any febrile patient residing in or returning from an endemic area should undergo a laboratory investigation. Chikungunya virus may be isolated from serum on days 2 through 4 of illness.68 Neutralizing antibody, hemagglutination inhibition activity, and complement fixation tests may be used to detect antibodies. Chikungunya virus–specific IgM antibodies may be found for 6 months or longer.69 O’nyong-nyong virus may be isolated by intracerebral injection into suckling mice, in which it produces alopecia, rash, and runting. Hemagglutination inhibition or complement fixation tests identify o’nyong-nyong virus.70,71 Because chikungunya and o’nyong-nyong viruses are closely related serologically, mouse antiserum raised to chikungunya virus or o’nyong-nyong virus react equally well with o’nyong-nyong virus, but o’nyong-nyong antiserum do not react well with chikungunya virus. Molecular detection methods have improved diagnostic specificity.72-75 Specific reverse transcriptase polymerase chain reaction–based assays have been developed for viral RNA detection.76,77

In chikungunya fever, synovial fluid shows decreased viscosity, poor mucin clot, and 2000 to 5000 white blood cells/mm³. Ross River virus has been isolated only from antibody-negative sera. In Australian epidemics before 1979, patients were antibody positive at the time of presentation. In contrast, patients during the Pacific island epidemics of 1979 to 1980 remained viremic and seronegative for up to 1 week after the onset of symptoms. Synovial fluid cell counts range from 1500 to 13,800 cells/mm³, predominantly monocytes and vacuolated macrophages.77 Barmah Forest virus infection is confirmed by rising titers of specific
infected patients have persistent arthralgias for months. Some have symptoms for as long as 5 to 6 years. Arthropathy may last 2 years or longer after onset. A smaller number of patients may develop residuals of chronic arthropathy. Case reports still have joint symptoms 1 year after infection.

After acute chikungunya fever, symptoms may persist for months before resolution. Approximately 10% of patients still have joint symptoms 1 year after infection. A few patients may develop chronic arthralgia. Case reports suggest that a few patients with chronic arthropathy develop destructive joint lesions, but a second process cannot be ruled out.

For persons with Ross River virus arthritis, mild exercise tends to improve joint symptoms. Half of all patients are able to resume their daily activities within 4 weeks, although residual polyarthritis may be present. Joint symptoms may recur. Arthralgia, myalgia, and lethargy may continue for at least 6 months in up to half of patients. Relapsing episodes gradually resolve, but joint symptoms have been reported in a few patients for up to 3 years.

Nonerosive chronic arthropathy is common after Sindbis virus infection, with up to one-third of patients having arthropathy 2 years or longer after onset. A smaller number have symptoms for as long as 5 to 6 years. Mayaro virus–infected patients have persistent arthralgias for months.

**Pathogenesis**

Little is known about the pathogenesis of chikungunya fever or arthritis. Involved skin shows erythrocyte extravasation from superficial capillaries and perivascular cuffing. The virus adsors to human platelets, causing aggregation, suggesting a mechanism for bleeding. Synovitis probably results from direct viral infection of synovium. In one patient with chronic arthropathy, the synovium appeared atrophic on arthroscopy and was histologically normal. The mechanisms of o’nyong-nyong virus pathogenesis are unknown. However, the virus was isolated from peripheral blood mononuclear cells in a patient in Chad.

Ross River virus antigen may be detected early in monocytes and macrophages by immunofluorescence, but intact virus is not identifiable by electron microscopy or cell culture. Erythematous and purpuric rashes show mild dermal perivascular mononuclear cell infiltrates, mostly T lymphocytes. Purpuric areas also show erythrocyte extravasation. Viral antigen may be detected in epithelial cells in erythematous and purpuric skin lesions and in perivascular zones in erythematous lesions.

Sindbis virus has been isolated from a skin vesicle in the absence of viremia. Skin lesions show perivascular edema, hemorrhage, lymphocytic infiltrates, and areas of necrosis. Anti-Sindbis virus IgM may persist for years, raising the possibility that Sindbis virus arthritis is associated with viral persistence.

**Treatment and Outcome**

Management is supportive. Nonsteroidal anti-inflammatory agents are useful, but aspirin should be avoided in view of the tendency for alphavirus rashes to develop a hemorrhagic component. Chloroquine has been used in chikungunya fever when nonsteroidal anti-inflammatory agents failed.

During the acute attack, range-of-motion exercises may decrease stiffness. In general, management of alphavirus infection is symptomatic; patients recover without sequelae. After acute chikungunya fever, symptoms may persist for months before resolution. Approximately 10% of patients still have joint symptoms 1 year after infection. A few patients may develop chronic arthralgia. Case reports suggest that a few patients with chronic arthropathy develop destructive joint lesions, but a second process cannot be ruled out.

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**HEPATITIS B VIRUS**

Hepatitis B virus (HBV), a member of the family Hepadnaviridae, genus Orthohepadnavirus, is an enveloped, double-stranded, icosahedral DNA virus measuring 42 nm in diameter.

**Epidemiology**

HBV occurs worldwide and is transmitted by parenteral and sexual routes. Prevalence is highest in Asia, the Middle East, and sub-Saharan Africa. In China, the prevalence is as high as 10%, compared with 0.01% in the United States. In endemic regions, infection occurs at an early age, frequently perinatally. Early HBV infection is usually asymptomatic. Rates of HBV carriage and specific antibody positivity decline with age. In the West, most infections are acquired during adulthood through sexual or needle exposure, leading to acute hepatitis. Of those with hepatitis, 5% to 10% develop persistent infection. In endemic regions, HBV is a common cause of chronic liver disease and a leading cause of hepatocellular carcinoma.

**Clinical Features**

The time from infection to clinical hepatitis is usually 45 to 120 days. A preicteric prodromal period lasts several days to a month and may be associated with fever, myalgia, malaise, anorexia, nausea, and vomiting. Joint involvement is usually sudden in onset and often severe, with symmetric and simultaneous involvement of several joints. Alternatively, arthritis may be migratory or additive. The joints of the hand and knee are most often affected, but wrists, ankles, elbows, shoulders, and other large joints may be involved as well. Fusiform swelling occurs in the small joints of the hand. Morning stiffness is common. Arthritis and urticaria may precede jaundice by days to weeks and may persist for several weeks, but they usually subside soon after the onset of clinical jaundice. Arthritis is usually limited to the preicteric prodrome. Those who develop chronic active hepatitis or chronic HBV viremia may have recurrent polyarthritis or polyarthralgia. Polyarteritis nodosa may be associated with chronic hepatitis B viremia.

**Diagnosis**

Urticaria in the presence of polyarthritis should suggest the possibility of HBV infection. Acute hepatitis may be asymptomatic, but elevated bilirubin and transaminases are usually present when arthritis appears. At the onset of arthritis, peak levels of serum hepatitis B surface antigen (HBsAg) are detectable. Virions, viral DNA, polymerase, and hepatitis B antigen may be detectable in serum. Anti–hepatitis B core antigen IgM antibodies indicate acute HBV infection rather than past or chronic infection.

**Pathogenesis**

Significant viremia occurs early in infection. Soluble immune complexes with circulating HBsAg form as anti-HBsAg antibodies are produced. An immune complex–mediated arthritis usually results, with immune complex...
deposition in synovium. Immune complexes containing HBsAg, antibody, and complement components may be detected.

HEPATITIS C VIRUS

Hepatitis C virus (HCV), a member of the family Flaviviridae, is an enveloped, single-stranded, spherical RNA virus measuring 38 to 50 nm in diameter.

Epidemiology

HCV infection occurs worldwide. Like HBV infection, seroprevalence is higher in Africa and Asia, where it may cause one-fourth of acute and chronic hepatitis cases. In Japan, up to 50% of hepatitides may be caused by HCV. In the United States, an estimated 2.7 million individuals are infected. More than half of all cases of non-A, non-B hepatitis are attributable to HCV infection. Multiple HCV genotypes and quasispecies are organized into six major groups. They differ in pathogenicity, severity of disease, and response to interferon.

Clinical Features

Acute HCV infection is usually benign. Up to 80% of post-transfusion infections are anicteric and asymptomatic. Liver enzyme elevations, when present, are usually minimal. Normal transaminase levels do not exclude HCV infection. Community-acquired cases may present more symptomatically and with significant transaminase elevations. Acute fulminant HCV hepatitis is rare. Acute HCV infection may be accompanied by acute-onset polyarthritis in a rheumatoid distribution, including the small joints of the hand, wrists, shoulders, knees, and hips.

HCV is often associated with mixed (type II and III) cryoglobulinemia. Essential mixed cryoglobulinemia—a triad of arthritis, palpable purpura, and cryoglobulinemia—is associated with HCV infection in most cases. Cryoglobulinemia in HCV infection is also seen in the absence of arthritis and purpura. Cryoglobulinemia may be associated with necrotizing vasculitis. The presence of anti-HCV antibodies in essential mixed cryoglobulinemia is associated with more severe cutaneous involvement, such as Raynaud’s phenomena, purpura, livedo, distal ulcers, and gangrene.

HCV RNA may be found in 75% of cryoprecipitates from patients with essential mixed cryoglobulinemia and anti-HCV antibodies.

Diagnosis

Serologic tests use an array of antigens in an enzyme immunoassay. A recombinant antigen strip immunoblot assay is confirmatory. Polymerase chain reaction–based diagnostics allow confirmation of HCV viremia, viral load, and genotype. A minority of patients may have HCV RNA detectable by polymerase chain reaction amplification methods in the absence of positive serologic findings. Liver biopsy for staging of liver disease is usually indicated in patients who have serum anti-HCV antibody or RNA, even in the setting of normal liver enzymes, because liver enzymes do not reflect liver histology. A number of algorithms based on blood measures of liver involvement have been proposed to aid in staging.

Pathogenesis

HCV infection persists despite antibody response to viral epitopes. Increased CD4+CD25+ regulatory T lymphocytes may blunt the immune response to HCV. A high rate of mutation in the envelope protein is responsible for the emergence of neutralization-escape mutants and quasispecies. HCV may contain an IgG Fc binding region on its surface; humoral immune response to HCV would, by epitope spreading, also target bound immunoglobulin Fc structures. Chronic HCV infection leads to cirrhosis, end-stage liver failure, and hepatocellular carcinoma after a period of up to 20 years, but the frequency of these sequelae is debated, and the mechanisms by which they occur are unknown.

Treatment

Initially, interferon-alfa2b was used to suppress viral titers and ameliorate HCV liver disease in about half of patients and may have benefited HCV-associated cryoglobulinemia. Relapse after completion of the initial course of therapy was common. The current use of pegylated interferons that increase drug half-life and decrease clearance, and the addition of ribavirin, have improved outcomes. Controversy continues regarding whether interferon therapy precipitates autoimmune diseases such as autoimmune thyroiditis. Those with cryoglobulinemia who fail interferon therapy require immunosuppressive therapy when vasculitis is present.

HUMAN T-LYMPHOTROPIC VIRUS TYPE 1

Human T-lymphotropic virus type 1 (HTLV-1), a retrovirus, is endemic in southern Japan, where it has been associated with oligoarthritis and a nodular rash. Human T-lymphotropic virus type 1 (HTLV) serology is positive. Type C viral particles are found in skin nodules. Synovial tissue is infiltrated by leukemic T lymphocytes with lobulated nuclei.

OTHER VIRUSES

Joint involvement occasionally occurs in numerous other commonly encountered viral syndromes. Children with varicella rarely develop brief monoarticular or pauciarticular arthritis. Mumps in adults is occasionally associated with small or large joint synovitis preceding or following the onset of parotitis by up to 4 weeks. Mumps arthritis may last several weeks. Infection with adenovirus and with coxsackieviruses A9, B2, B3, B4, and B6 has been associated with recurrent episodes of polyarthritis, pleuritis, myalgia, rash, pharyngitis, myocarditis, and leukocytosis. Epstein-Barr virus–induced mononucleosis is frequently accompanied by polyarthralgia, but monoarticular knee arthritis sometimes occurs. A few cases of polyarthritis, fever, and myalgia due to echovirus 9 infection have been reported.
Arthritis associated with herpes simplex virus or cytomegalovirus infection is rare, but a severe cytomegalovirus polyarthritis has been described in several immunocompromised bone marrow transplant recipients.\(^{13}\) Herpes hominis occasionally causes arthritis of the knee in wrestlers, a condition referred to as herpes gladiatorum.\(^{14}\) Knee arthritis has been reported as a rare complication after vaccinia inoculation.\(^{15}\)

Selected References

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Full references for this chapter can be found on www.expertconsult.com.
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