Parvovirus

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Name of Virus: Parvovirus

16.1 Brief Introduction

Parvovirus (PV), one of the smallest viral pathogens, derives its name from the Latin *parvum*, meaning small. Discovered in 1974 by researchers studying viral hepatitis (Cossart et al. 1975), parvoviruses are important human and animal pathogens. The virus, an Erythrovirus propagates best within erythroid progenitor cells (Brown et al. 1993). In humans, the cellular receptor P antigen for parvovirus B19s may cause erythema infectiosum, an entity also called "fifth disease" (recognized in 1889 and named in 1899). Its name given to it historically as the fifth disease, after measles, rubella, varicella, and scarlet fever of the classical childhood skin rashes or exanthems in children (David 1982; Plummer et al. 1985; Brown et al. 1993).

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Parvovirus infection is more common in children than adults. About 20 % of those infected will be asymptomatic and 50 % will experience nonspecific flu-like symptoms. PV can cause serious illnesses including pneumonia with diffuse alveolar damage resulting in acute respiratory distress syndrome, major joint arthritis, life-threatening transient aplastic crisis especially in patients with underlying sickle cell disease, and hemolytic disease such as chronic red cell aplasia in immunocompromised patients (Smith-Whitley et al. 2004). It may also cause early fetal death or hydrops fetalis and unrecognized viral myocarditis (Young and Brown 2004). Lung involvement is uncommon but has been reported to occur in children with fatal multiorgan failure (Ferraz 2005). Pleuropneumonitis due to PV can be seen in immunocompromised adults with heart-lung transplants (Janner et al. 1994; Castagna et al. 2011) but may also be seen in sporadic non-immunocompromised patients (Wardeh and Marik 1998; Morris and Smilack 1998). The multiplicity of clinical presentations of the infection can masquerade as other disorders, in all ages resulting in misdiagnosis and possible overtreatment.

16.2 Synonyms

Fifth disease, Nakatani virus, Erythema infectiosum, Slapped cheek syndrome, Apple sickness, Butterfly pox

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16.3 Classification

Family – *Parvoviridae*
Genus – *Erythrovirus*

16.4 Epidemiology

Infection by PV occurs worldwide with similar infectivity rates in the USA, Europe, and Asia (Norja et al. 2008). By age of 15 years, over 50 % of adolescents have antibodies from previous childhood infection (Young and Brown 2004). The number of people infected over adulthood increases so that the majority of elderly individuals are seropositive (Kerr 1996). Studies of fifth disease outbreaks in the UK have shown that many children, and adults had evidence of PV antibodies but not the symptoms of the disease (Anderson et al. 1983). In temperate climates, infections peak in late winter or early spring with sporadic small epidemics (Cohen and Buckley 1988). PV B19 spreads through respiratory droplets and is highly contagious (Anderson et al. 1985). Household transmission is >50 % and 20–30 % for teachers and day-care providers. As it lacks a lipid envelope and has high genomic stability, the PV is difficult to kill and is resistant to heat and solvent detergents (Kaufmann et al. 2004). PV infection has been reported as a nosocomial infection with transmission via blood products (especially pooled factors VIII and IX) and in health-care workers from patients and contaminated specimens (Kooistra et al. 2011) (Seng et al. 1994) (Siegl and Cassinotti 1998). PV is transmitted vertically from infected mothers to fetuses with a 30 % risk of transplacental transmission. PVB19 is the predominant pathogen and is the prototype strain for genotype 1 (Failey et al. 1995; Jordan et al. 2001). Less common, recently discovered erythroviruses (genotypes 2 and 3) are increasing and spreading. Genotypes 1 and 2 are typically present in Western countries (the USA and Europe) and genotype 3 in sub-Saharan Africa and South America (Freitas et al. 2008).

16.5 Ultrastructure

Parvovirus B19 is a 26 nm, non-enveloped 5.6 kb single-stranded DNA virus. The capsid consists of two structural proteins (VP1 and VP2) which arise from alternative splicing, therefore VP1 and VP 2 are similar except VP2 contains an additional 226 amino acids. In addition, PV has one nonstructural protein (NSI). Importantly PV has P blood group antigen cellular receptor (globoside) (Heegaard and Brown 2002). The translation machinery of PV is all in the cytoplasm, and then the proteins home back in the nucleus for viral assembly.

16.6 Immunology

Parvovirus is demonstratable in the bloodstream some 7–10 days after exposure and persists for approximately 5 days with viral loads exceeding 10^{12} particles/ml of blood. Parvovirus B19-specific IgM antibodies are at a detectable range within 10–12 days and persist for about 3–5 months. IgG antibodies are seen 15 days postinfection and can persist for long periods. Usually, the patient will have lifelong immunity (De Haan et al. 2007). An effective immune response is only seen if VP1 antibodies are present. Isa et al. have shown a cell-mediated immune response with production of interferon (IFN)-gamma, interleukin (IL)-2, IL-6, and tumor necrosis factor (TNF)-alpha (Isa et al. 2007).

16.7 Clinical Features

A relatively small percent of patients (25 %) may be infected but remain totally asymptomatic. However, asymptomatic patients are still capable of spreading the disease. In about 75 % of non-immunocompromised patients that exhibit symptoms, there are symptoms of an upper respiratory infection or flu-like illness with fever, runny nose, nausea, and headache (Mandel 2009). After several days, some patients (up to 25 %) develop a red rash on their face which is felt to be related

to the formation and deposition of immune complexes (Young and Brown 2004). After several days, the rash may spread and may then appear on the chest, back, buttocks, and extremities. On the soles of the feet, the rash may be especially pruritic (Sharad and Kapur 2005). The rash clears in a week or two, and when it begins to resolve, it may appear "lacy" in appearance. The rash may be very "fleeting" (<24 h), but recurrences may be induced by exposure to sunlight, heat, emotion, or strenuous exercise. Older infected children may also have lymphadenopathy and an atypical rash (Broliden et al. 2006).

In adults, especially middle-aged women, joint pain and swelling (immune-mediated polyarthropathy) may appear involving the joints of the hands, feet, or knees (Moore 2000). Joint symptoms can be seen in 8 % of children and 60 % of infected adults. This may be the only manifestation of the infection in these patients. The inflammatory joint symptoms may persist for weeks to months but usually resolve without long-term damage (Tello-Winniczuk et al. 2011; Naides et al. 1990; Kerr et al. 1995). There have been scattered reported cases of fibromyalgia symptoms linked to PVB19 via IgM serology (Buyukkose et al. 2009). A causal relationship with fibromyalgia is uncertain as the PV infection may be incidental, in some cases.

PVB19 affects 1–5 % of pregnant women with most women having a normal pregnancy outcome (Ergaz and Ornoy 2006). There are documented relationships with fetal deaths secondary to possible fetal anemia with resultant fetal high-output cardiac failure and nonimmune hydrops fetalis (Adler and Koch 2011). Intrauterine PVB19 has an affinity for the P antigen expressed on fetal cardiac myocytes leading to cardiac failure from direct or indirect or autoimmune damage (Bowles et al 2003). There have been isolations of PVB19 in children and adults with unexplained fulminant hepatitis. These patients had a low bilirubin level, no jaundice, and recovered rapidly. Serum high values of AST and ALT normalized in 3 weeks (Huang et al. 2012).

The most recognized serious disease associated with PVB19 is aplastic crisis which may be life threatening. In patients with increased red blood cell (RBC) turnover from other disorders such as (sickle cell disease, hereditary spherocytosis), PV infection can result in an abrupt cessation of RBC production due to infection of erythroid progenitor cells in the bone marrow. This may result in severe anemia with congestive heart failure or stroke. Patients may also develop pancytopenia with thrombocytopenia. With clearance of the virus, the crisis will abate. In patients who are immunocompromised, the lack of immunity results in persistent infection and chronic pure red cell aplasia (Posfay-Barbe and Michaels 2003). PVB19-associated pure red cell aplasia has been the first presentation for HIV-infected patients (Koduri 2000).

In rare cases of PV-related fulminant pulmonary failure, patients may present with a sudden onset of respiratory distress (Ferraz et al. 2005). Bronchoscopy may only reveal mild mucosal erythema with mild increase in secretions. Diffuse bilateral parenchymal opacities with or without effusions can be seen on chest radiography (Berjaoui et al. 2006). Other PV symptoms may or may not be seen including rash, arthropathy, and transient anemia symptoms. In patients receiving stem cell transplant, PV B19 pneumonia may be misdiagnosed as another viral or opportunistic infection, and serology screening is imperative in order to avoid missing acute infection.

16.8 Pathologic Changes

Skin lesions when biopsied to exclude other diseases usually have a nonspecific histologic picture (Katta 2002). There may be interstitial histiocytic infiltrates with piecemeal fragmentation of collagen and a mononuclear cell-predominant vascular injury pattern. Other features include an interface dermatitis, eczematous alterations, and papillary dermal edema (Bonvivini et al. 2010). The pathology of cutaneous B19 infection suggests tissue injury mediated by delayed-type hypersensitivity, by antibody-dependent cellular immunity directed at microbial

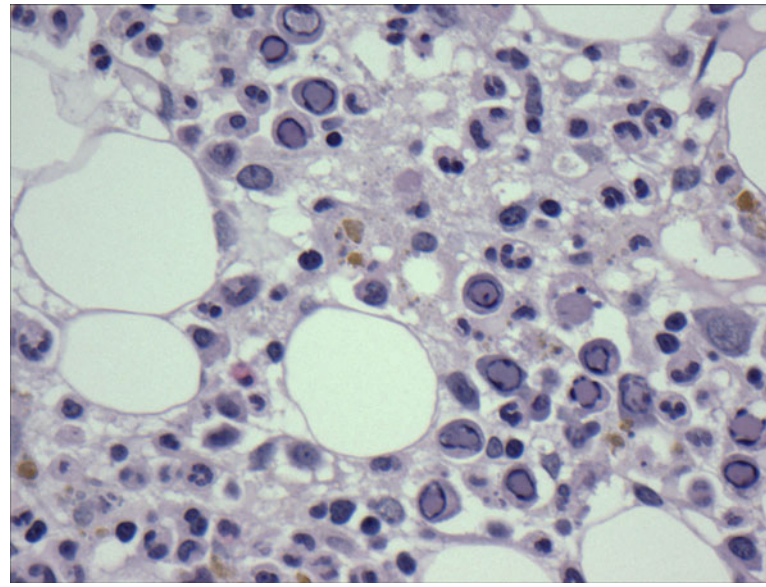

Fig. 16.1 Parvovirus infections in the lung are similar to those shown in other organs. This illustration shows the bone marrow of an immunocompromised patient. Note eosinophilic inclusions within early erythroid forms. Hematoxylin and eosin (Courtesy of Dr. Richard L. Kradin, Massachusetts General Hospital, with permission from Diagnostic Pathology of Infectious Disease, 2010, Saunders-Elsevier, Publishers)

antigenic targets in the epidermis and endothelium, and by circulating immune complexes in the setting of leukocytoclastic vasculitis (Magro et al. 2000). In patients with transient aplastic crisis, the bone marrow will have erythroid hypoplasia and occasional giant erythroblasts and may rarely have proerythoid cells with intranuclear viral inclusions (Crook et al. 2000). In infected fetuses, there are many erythroid precursor cells with eosinophilic inclusions which compress the nuclear chromatin against the nuclear membrane in the placenta and fetal tissues (Morey et al. 1992).

In patients with pulmonary manifestations, bronchioloalveolar lavage at bronchoscopy may show a lymphocyte-rich effusion. Such effusions may also be seen in autoimmune diseases and viral pneumonias. Desquamated balls of reactive type II pneumocytes may be abundant with large nuclei with increased nuclear to cytoplasmic ratios, prominent clumped chromatin and large round to irregular nucleoli, and eosinophilic inclusions (Fig. 16.1). The lungs may show classic changes of diffuse alveolar damage with hyaline membranes, reactive type II pneumocytes, and lymphocytic infiltrates (Beske et al 2007). In acute presentations, the lungs may show intra-alveolar hemorrhage due to weakened and damaged intraseptal capillaries. Viral inclusions are extremely difficult to find except in rare patients who are immunocompromised. Immunohistochemistry is however helpful highlighting infected cells (Fig. 16.2). The diagnosis is based on serological rise of PV IgM and DNA evidence of PV from lung biopsy or cytologic specimens (Berjaoui et al. 2006). The exact pathogenesis of severe pulmonary complications by B19 is not understood but may be related to a cytotoxic effect of the virus directly or indirectly on the interstitial endothelial cells. An aberrant host immune response triggered by B19 may also contribute to the pulmonary pathology (Magro et al. 2006). The lung tissues are not the preferred site for virus replication in humans or other mammals. This is why PV B19 pneumonia is very rare or unrecognized. B19 DNA may persist perpetually in human tissues such as skin, synovial cells, and hepatocytes. The significance of a positive PCR for PV B19 may be related to the amount observed. Since it may be harbored in healthy tissues, PCR detection of PV B19 during an illness may not be definitive proof that PV is the cause of the lung injury unless other causes are excluded. In immunocompromised patients with PV B19 pneumonia, it is difficult to determine if it is a new infection associated with viremia or a reactivation of virus dormant within the lung tissues. In fact, simultaneous infection with two

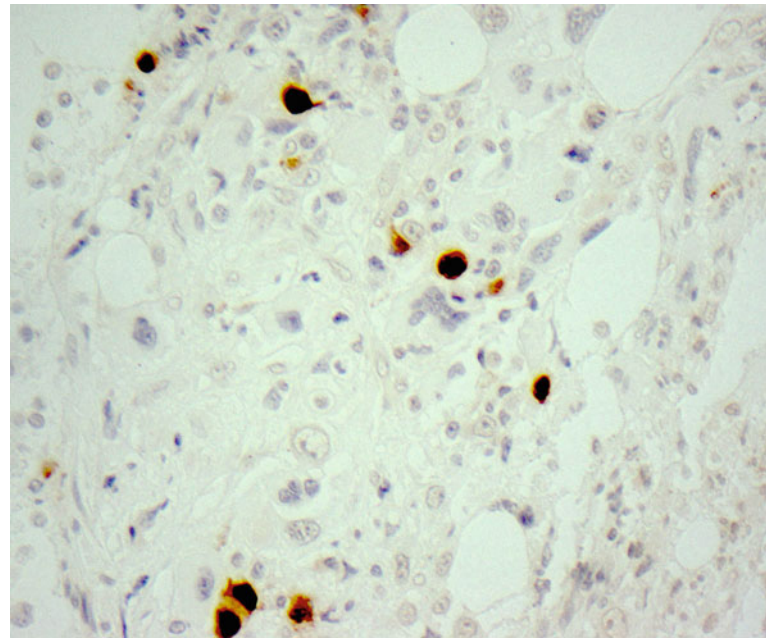

Fig. 16.2
Immunohistochemical stain for parvovirus highlights viral inclusions and confirms the diagnosis. Immunoperoxidase (Courtesy of Dr. Richard L. Kradin, Massachusetts General Hospital, with permission from Diagnostic Pathology of Infectious Disease, 2010, Saunders-Elsevier, Publishers)

pathogens often results in enhanced morbidity and mortality, in particular in immunocompromised patients (Broliden 2001).

16.9 Diagnosis

In immunocompetent patients, the diagnosis is based on the presence of IgM antibodies (Knipe and Howley 2007). The presence of IgG alone may only suggest previous infection. The virus can be detected by the polymerase chain reaction (PCR) assay for months to years after infection. There may be a transient drop in the reticulocyte count and hemoglobulin concentration in week 1 or 2, but the numbers normalize after a month (Doyle et al. 2000).

In acute lung involvement, the diagnosis may be easily missed and misinterpreted as vasculitis or an autoimmune disease or another etiology. Suspicion is needed to determine if PV is the cause of the respiratory failure using serology and DNA evidence of PV infection. This may be difficult because IgM may be persistent from a previous self-limited infection and PV DNA can persist for months. PV is a very prevalent disease in the general population and has been demonstrated in several types of lung damage patterns thought to possibly be related to the ANCA-positive vasculitic syndromes associated with PV. PV has also been reported in idiopathic interstitial pulmonary fibrosis and may be related to capillary damage. PV has a known affinity for capillary endothelium (Magro et al. 2006).

16.10 Differential Diagnosis

PV symptoms prior to the appearance of the rash are nonspecific and thought to represent influenza or a rhinoviral infection. If the rash appears, in children it can be mistaken for rubella. The polyarthropathy can be confused with rheumatoid arthritis especially since patients may have a transient increase in serum rheumatoid factor (Tello-Winniczuk et al. 2011).

PVB19 can be misdiagnosed as Systemic Lupus Erythematosus (SLE). In an initial presentation of a patient, the symptoms of PVB19 may overlap greatly with SLE. Both PVB19 and SLE patients may have cytopenia, anti-DNA antibodies, antinuclear antibodies (ANA), and hypocomplementemia. However, patients with PVB19 will have symptom resolution in several weeks.

There may be an increase of infections with PVB19 in patients with known SLE due to intrinsic immunosuppression or immunosuppressive therapies, with lower levels of circulating PV IgM and IgG (Bengtsson et al. 2000). In the lung, the changes may be similar to collagen vascular diseases, infections due to other viruses, and even lepidic adenocarcinoma. The differential diagnosis includes many entities which may cause acute respiratory distress syndrome. The transient or rapid anemia with or without skin rash can help in recognizing the infection. Because PV can create an environment with lower resistance to other opportunistic pathogens, a concurrent fungal or bacterial pneumonia may overshadow the effects of PV B19.

16.11 Prevention

Prevention of acute illness is often difficult. When outbreaks are recognized, decrease of exposure to body fluids of the infected patient is useful. Recognized viral illness with fevers and rashes in children should result in their removal from the day-care or school environment (Leppard et al. 2007). Disinfection is not always effective due to the hardiness of the virus. The US Food and Drug Administration (FDA) issued a recommendation in July 2009 that makers of plasma-derived products (which include plasma-derived factor VIII and factor IX concentrates) begin screening for human PVB19 by performing nucleic acid testing.

16.12 Treatment and Outcome

Treatment is symptomatic in most cases. Other treatments related to the varied clinical symptoms may include blood transfusions for aplastic crisis or intrauterine infections. Intravenous immunoglobulin may be used in immunocompromised patients or in placental exchanges of infected pregnant women with fetal distress (Kurtzman et al. 1989; Mouthon et al. 2005). Antiretroviral therapies are important in HIV patients to prevent aplastic crisis. In patients with lung involvement, early recognition is needed for provided pulmonary support, antiviral therapies, and antibiotics to prevent secondary bacterial infections which may result in sepsis and demise. Despite these measures, the disease may be fatal, especially if the patient is immunocompromised.

16.13 Vaccination

Effective vaccines are available for animal strains of PV, but currently, there is no approved vaccine available for humans. There is progress for their development and use in young children. Technology to express viral proteins VP1 and VP2, derived from a copy of the parvovirus B-19 genome (strain Au) obtained from a child with sickle cell disease and transient aplastic crisis, was developed at the National Heart, Lung, and Blood Institute. Individual viral proteins were expressed in a baculovirus system and, when recombinant vectors are cotransfected into insect cells, VP1 and VP2 spontaneously assemble into empty viral-like particles. The vaccine consists of two viral proteins (VP1 and VP2) in separate baculovirus vectors that are coinfected at the correct multiplicity of infections (MOIs) into Spodoptera frugiperda (Sf9) cells and that, upon expression, self-assemble into immunogenic viruslike particles. Phase 1 trials have been completed, but mass production is needed for testing (Bernstein et al. 2011).

16.14 Clinicopathologic Capsule

A common childhood disease which is often unrecognized, parvovirus infection causes an influenza-like illness which can be associated with a rash known as erythema infectiosum (fifth disease). Ultrastructurally, the viral agent, a member of the family Parvoviridae, is a small single-stranded DNA virus that uniquely infects human erythroid progenitor cells. The clinical presentations may vary from irritative (upper respiratory infections and rashes) to severe (diffuse alveolar damage with ARDS, arthropathy, cardiomyopathy, fulminant hepatitis, hydrops

fetalis, and aplastic crisis). A definitive diagnosis can be made with detection of IgM by serology and specific PVB19 DNA PCR. A previous infection results in lifelong immunity unless the patient is immunocompromised.

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