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Parvovirus B19: Past, Present and Future

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Review Article

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ABSTRACT

Parvovirus B19 (B19V) is a world-wide distributed virus member of the *Parvoviridae* family, generae Erythrovirus. It causes a wide list of diseases whose pathological mechanisms are majorly unknown. Many theories have emerged in an attempt to explain the pathogenics of B19V in each of its target organs, most interestingly in bone marrow, myocardium, and endothelium. Persistent infection in these organs allows the virus to infect cells despite presence of adequate antibodies formation. Developing from all over the world report that B19V is encountered in an ever changing manner variety of clinical entities. This new understanding opens the doors to future developments amid of a yet to be discover pathogenesis.

INTRODUCTION

Parvoviruses are small nonenveloped icosahedral viruses with linear single-stranded DNA genomes of 4.5 to 5.5 kb which infect a variety of mammals, and are associated with a wide spectrum of acute and chronic diseases in humans, ranging from the erythema infectiosum to more complex diseases as arthropathies, critical failures of red cell production, hydrops fetalis, fetal loss, miocarditis or hepatitis [1-3].

Parvovirus B19 was discovered in a serum with haemagglutinating activity (serum no. 19 in line B) in 1975. It was until 1983 that it was proven to cause a disease: the eritema infectiosum. It is a member of the family *Parvoviridae*, subfamily Parvovirinae. Based on its biological characteristics, the subfamily is subdivided into three generae: Parvovirus, Erythrovirus, and Dependovirus. Parvovirus B19 is the only accepted member of the Erythrovirus genus. It is a non-enveloped, single-stranded DNA virus and one of the smallest viruses known to infect mammalian cells.

B19 viruses are now formally subdivided into three genotypes, the prototype genotype 1 and the two variant genotypes 2 and 3, and further subtypes. Of relevance, all genotype variants can be contaminants of blood and blood-derived products, so mandatory screening for removal of high-titer blood units from manufacture processes must be able to detect all genotypes. All B19V genotypes appear to co-circulate, but their relative frequencies are remarkably different. Genotype 1a has a ubiquitous distribution being responsible for the majority of human infections worldwide. Genotype 2 (prototypes LaLi and A6) has been identified at very low frequency in viremic individuals in Europe, Brazil, and Vietnam. Genotypes 3a and 3b are detected at higher frequencies in Western Africa and at lower frequencies in other parts of the World.

Nine mRNA have been identified to transcript during replication and encode the VP1 and VP2 proteins. The capsid consists of 60 structural subunits, 95% of which are a major viral protein (VP1) that differs from the other major viral protein VP2 in a unique N-terminal region composed of 227 additional amino acids. The viral genome (5 kbp) encodes for three major proteins, the non-structural protein 1 (NS1) and the viral capsid proteins (VP1 and VP2) [4-7].

B19V is a cosmopolitanly distributed virus. Studies in Germany found that 10-20% of children >3 years of age had undergone infection, and individuals from 10 to 19 years old showed antibodies against B19V without recalling symptoms. By the age of 15, about 50% of individuals have serologic evidence of a past infection, which may present as the common childhood disease erythema infectiosum. At the age of 70, seroprevalence reaches 80 to 100% [2,8-12]. The virus is transmitted mainly via the saliva or by droplet infection. However, the infection may also be transmitted vertically from mother to fetus, or organ transplantation. In

addition, transfusion of blood components (in particular packed red cells from blood collected during the short pre-seroconversion viremic phase) had been linked to transmission of B19V. Examinations of blood donors revealed an average seroprevalence of 60%. According to a study made in pregnant women new infections through blood transfusions can be estimated at up to 0.5–1.0% per year [1,13].

A spectrum of blood infectious agent is transmitted through transfusion of infected blood donated by apparently healthy and asyntomatic blood donors, For example, West Nile virus, chikungunya, babesia, dengue, hepatitis E virus and ocacionalmente a variant of Creutzfeldt-Jakob disease [14]. A number of studies on B19V prevalence in donor populations from various countries have been published confirming the above. A direct comparison of such epidemiological studies is often not possible since the test methods (counter flow electrophoresis, dotblot, and various PCR methods) may differ in their sensitivity and seasonally, furthermore, local outbreaks may influence the results. Approximately 31 million donations (predominantly from the USA and Germany) were examined in the past 7 years (starting in 2000), and a frequency of 1:6,200 B19V DNA (>2 x 10^6 geq/ml) was identified in the donations. The prevalence of genotype 3 also seems to be low in the European population. However, it should be noted that the commercial NAT systems currently available do not safely detect genotype 3, and genotype 2 might be only partially detected. Genotype 3 was identified in one plasma donation in the USA [1,5-18].

Primary infection with B19 can cause aplastic crises in individuals with high red cell turnover and chronic red cell aplasia, or even severe pancytopenia in immunocompromised individuals.

The virus is resistant to inactivation used in the procurement of blood and hematopoietic stem cell products, leading to a known risk of B19 transmission [13].

Due to the difficulty in removing and inactivating B19V, the most effective measure for mitigating the rusk of B19V transmission through plasma derivatives should be limiting the virus load in the manufacturing plasma pools and discard donations with high titer B19v DNA seems to be necessary [18].

PERSISTENT INFECTIONS

A transient high level viremia is present for less than a week. Then it declines with the appearance of specific IgM antibodies that can be detected for 8 to 10 weeks. After that, specific IgG antibodies are present for the lifetime of the individual.

Following acute infection, B19V persists in many different tissues, including skin, bone marrow, synovium, and liver, and it is believed that this is a lifelong phenomenon. The possibility of B19 integration into the human genome has not been confirmed, although the human genome does exhibit short footprints of the B19 genome in multiple human genes, the significance of which remains unclear [19,20].

Persistent infections may be observed in immunocompromised patients unable to produce neutralizing antibodies and to clear the virus. This leads to chronic carriage of B19V with or without anemia. Low DNA titers can remain in the blood for 6–12 months. Lifelong protection against B19V persistence of infection in the bone marrow has been reported in immunocompetent individuals with or without symptoms.

The mechanism by which the virus enters chronic carriage remains unexplain but few theories have emerged. Molecular mimicry of viral epitopes by cellular autoantigens and the production of anti-idiotype antibodies could participate in the production of self-antibodies. Recently, reproductive B19V infection of endothelial cells has been obtained *in vitro*. The stimulation and/or persistent infection of such cells could play a role in the pathogenesis of virus [21].

The oxygen level in human bone marrow, which is much lower than that of *in vitro* cell culture conditions. Chen et al. reported a significant enhancement of B19V DNA replication, as well as progeny virus production has beem observed during B19V infection of hEPCs when they are cultured under 1% 0_2 (hypoxia) [22,23]. It has been suggested that erythrocyte P antigen functions as the receptor for B19V virus infection of target erythroid cells [24], hepatocytes, and other cells that possess globosides and glycosphingolipids in their cell membrane. Nevertheless, it can only replicate in the erythroid precursors and few other cells including: fetal liver, isolated stem, bone marrow cells, and megakaryocytic leukemia cell lines maintained with erythropoietin. Infection with parvovirus B19V should be considered in the differential diagnosis in both immunocompromised and immunocompetent patients presenting acute hepatitis of unknown etiology particularly in cases of underlying hemolytic diseases and immunodeficient host with aplastic anemia [25].

DIAGNOSIS

The quantitative PCR (qPCR) assay analytical performances have been determined on the 1st WHO International Reference Panel for Parvovirus B19 genotypes. The developed qPCR protocols allow for the detection of genotypes 1 to 3 with equal accuracy, and with a limit of detection (LOD) of 200 IU/ml.

Because the ability to diagnose viral infection has improved with the advent of molecular biology techniques, case reports and series have associated DCM with about 20 viruses. As the prevalence of enteroviruses decreased, the prevalence of adenovirus increased after 1995. More recently, parvovirus B19 has been the most commonly detected viral genome [26].

Detectable levels of parvovirus B19-specific IgM can be found within 7 to 10 days of virus exposure and remain measurable for approximately two to three months before diminishing. IgG antibodies usually appear after two weeks of infection and persist for life [27]. B19V can be cultured in erythroid progenitor cells from a variety of sources, including human BM, fetal liver, umbilical blood, and peripheral blood. The most accurate diagnostic method for parvovirus B19V infection is the nucleic acid detection by PCR [28].

Determination of B19V viral load represents an alternative approach to serology for staging of B19V infection. High viremia levels of B19V are associated with recent infection. However, in immunocompetent individuals, low levels of B19V DNA may persist for months or even years. It is important that the qPCR used is able to detect B19V genotypes 1, 2, and 3, but many commercial and in-house PCR methods have shown lower sensitivity or failure to detect genotypes 2 and 3 [14].

Clinical implications

The spectrum of B19V disease covers almost any organ. 25% of infected people never recall having symptoms. Human parvovirus B19 infections may cause a widespread benign and self-limiting disease in children and adults, (erythema infectiosum of fifth disease).

Additionally, a variety of further manifestations are associated with the infection such arthralgias, arthritis, leucopenia and thrombocytopenia, anemia and vasculitis, spontaneous abortion and hydrops fetalis in pregnant women, also neurologic disease, myocarditis and hepatitis. So, B19V capsid RNA or proteins have been reported in bone marrow, colon, heart, liver, lymphoid, synovial, testicular, and thyroid tissues. In a sub-set of these cases, B19V capsid mRNA or proteins have been associated with increased inflammatory-related gene expression [3,28,30].

Erythema infectiosum

Also known as the fifth disease is the most prevalent disease manifested by B19V. Prodromal symptoms are mainly unnoticed and include fever, coryza, headache and nausea. The characteristic “slapped cheek” erythema begins in face and diseminates after one to four days to the trunk and limbs. The disease is self- limited [3,31].

Eriyhema infectiosum and arthropathy need no more than symptomatic treatment with antiinflamatory drugs.

Arthropathy and autoimmune phenomena

Arthropathy is the most common manifestation in adults. It affects as much as 60% of females and 30% of males. The clinical course and immune response are biphasic and a second phase of symptoms presents with rash, itchiness or arthralgia about 17–18 days after inoculation. It is an autoimmune mediated disease that affects primarily carpophalangeal joints, knees, wrist and ankles. Despite being isolated in sinovial fluid, there is not a convincing link to chronic erosion of joints [1].

VIRUS AND AUTOIMMUNITY

1) Both in children and adults parvovirus B19 infections have been frequently implicated as a cause or trigger of various forms of autoimmune diseases affecting joints, connective tissue and large and small vessels. In addition, autoimmune neutropenia, thrombocytopenia and hemolytic anemia are known as sequelae of B19 infection. Human parvovirus B19 (B19V) is known to induce apoptosis that has been associated with a variety of autoimmune disorders [32].

2) B19V induced chronic disease and persistent infection suggests B19V can serve as a model for viral host interactions and the role of viruses in the pathogenesis of autoimmune diseases.

The non-structural protein 1 (NS 1) of B19V induces apoptosis in non-permissive cells lines and that this protein can cleave host DNA as well as form NS1-DNA adducts. In particular, signature self-antigens such as Smith, ApoH, DNA, histone H4 and phosphatidylserine associated with autoimmunity were present in these ApoBods. This suggests that B19V can produce a source of self-antigens for immune cell processing. The results support the hypothesis that B19V NS1-DNA adducts, and nucleosomal and lysosomal antigens present in ApoBods created in non-permissive cell lines, are a source of self-antigens [33].

3) B19 infection may simulate both clinical and laboratory features of SLE, presenting either as a potential first time diagnosis of SLE or as an exacerbation of previously established disease. The similarities in both clinical and serological features of parvovirus infection and SLE at presentation may hinder the differential diagnosis between these two conditions. Hence, parvovirus B19 infection mimicking SLE usually fulfills <4 ACR criteria for SLE, rarely includes cardiac or renal involvement or presents with haemolytic anaemia, and is usually associated with short-lived, low titers of autoantibodies [34].

4) More than 5% of over 800 monoclonal antibodies derived from multiple RNA and DNA viruses, as well as from a large number of T cell clones, engage in such interactions. Several of these cross-reactions, (molecular mimicry), are against unique host proteins involved in autoimmune responses and diseases. Thus, molecular mimicry initiated as a host response to a virus or a microbial infection, but alternatively cross-reacting with an appropriate host-antigen, can be a mechanism for instigating an autoimmune disease [35].

5) Lunardi et al. identified a peptide that shares homology with parvovirus VP1 protein and with human cytokeratin. Moreover

the VP peptide shares similarity with the transcription factor GATA1 that plays an essential role in megakaryopoiesis and in erythropoiesis. These new data sustain the role played by molecular mimicry in the induction of cross-reactive (auto) antibodies by B19V infection [36].

Proving cause and effect for human disease is difficult. Nevertheless, an accumulation over the last three decades of clear associations between sequence homology and T and B cell cross-reactivity between selected host antigens identified as essential for the development of autoimmune diseases and microbial agents strongly supports a causative role for molecular mimicry in that process. Molecular mimicry is but one mechanism for the development of autoimmune disorders occurring in association with infectious agents [35].

The molecular basis of the autoimmune phenomena is unclear. The involvement of the molecular mimicry between cellular and viral proteins, the induction of enhanced cytokine production via the viral transactivator protein NS1 and the phospholipase A2-like activity of the capsid protein VP1 may contribute to the induction of autoimmune reactions [29].

Getts et al. reported other infection-related autoimmunity hypotheses. An over-aberrant antiviral immune response may result in the liberation of self-antigen(s) not usually exposed to the immune system. Bystander T-cell activation may result from these antigens being taken up, processed, and presented by local and inflammatory monocyte-derived APCs to autoreactive T cells [37].

Finally, consider that Rheumatoid arthritis (RA) is an immune disease with unknown etiology. Previous research indicates that anti–citrullinated protein antibodies (ACPAs) are implicated in the pathogenesis of RA. Antibody titers show a marked increase near 2 years prior to RA diagnosis, suggesting a second event during some stage in the preclinical phase. Interestingly, this is also the time at which IgM-RF is usually detected. IgM-RF has been shown to appear a median of 2 years prior to clinical symptoms, which might be due to a variety of factors.

Detection of emerging arthritogenic viruses has changed the epidemiology of infection-related arthritis. The role of viruses in the pathogenesis of chronic inflammatory arthritides such as rheumatoid arthritis is increasingly being recognized, a role for Epstein-Barr Virus (EBV) infection in the etiology of autoimmune diseases, including rheumatoid arthritis (RA), has long been suggested and recently chronic manifestations of Chikungunya virus (CHIKV) infection may resemble those of some autoimmune connective tissue diseases. Furthermore, CHIKV infection can cause cryoglobulinemia and may induce rheumatoid arthritis and seronegative spondyloarthropathies in genetically susceptible individuals [38-40].

HYDROPS FETALIS

Fetal infection B19V is a leading cause of abortion and miscarriage. The transplacental transmission is estimated at 24 to 33%. Besides hydrops, B19V also causes congenital anemia, cardiac failure, impaired circulation and death [3].

Acute B19V infection occurs in 1–5% women during pregnancy, and the prevalence increases to 3–20% during epidemics. Approximately, 30-50% of pregnant women are non-immune and vertical transmission is common following maternal infection in pregnancy, most fetuses develop normally. However, maternal infection during the first 20 weeks of pregnancy may be associated with severe anemia, non-immune hydrops fetalis and fetal loss in up to 9% if undiagnosed and untreated [31,41,42].

In pregnant women who are immunocompromised or suffering from pre-existing hematological conditions, or infected fetuses where there is widespread tissue inflammation and red-cell destruction, fetal death may occur [30].

HEPATITIS

B19V damage to the virus has been rarely reported, presenting as an acute form [3]. Acute fulminant liver failure (AFLF) is a potentially fatal disease that may occur as a result of hepatic infection, toxic damage, or liver transplantation complications. Over one-third of idiopathic AFLF cases are accompanied by aplastic crisis. Brian Poole in 2004 suggests a mechanism by which B19V induces apoptosis through a caspase 3-dependent pathway. Caspase 8 activity is not necessary for B19 virus-induced apoptosis [10,11,42,43].

CANCER

Biopsies of tissues from synovium, skin, tonsils and liver showed the presence of B19V genome; and the persistence of B19V genome mainly denotes latent infection. Usually, detection of the persistence of viral genome with expressed viral proteins in the tumour cells indicates a productive infection of the virus in the cells and the potential involvement of virus in pathways leading to the development and/or progression of cancer [44,45].

Parvovirus B19 nucleic acids commonly exist in human colon tissues and VP1/VP2 antigen is preferentially located in colon polyps and adenocarcinomas lesions. B19 viral products VP1u may induce important oncogenic pathways in colon-cancer cells [46].

A sample of 119 paraffin-embedded specimens of colon polyps, adenocarcinomas, carcinoma-adjacent tissues, and normal controls were processed for nested polymerase chain reaction (PCR), in situ hybridization (ISH), immunohistochemistry (IHC), and laser capture micro dissection detection of B19V DNA and protein. The result was B19V DNA was detected in 94.6% of colon adenocarcinomas,

67.6 % of adjacent noncancerous tissues, 85 % of polyps, and 60 % of normal controls by nested PCR, respectively. This finding indicates that an association may exist between B19V infection and the development of colon neoplasia [44-46].

The pathogenetic role of B19V has still not been understood. It is not clear whether productive virus replication occurs in the tissues affected (endothelium, myocardium) or whether secondary mechanisms plays a role (e.g. antigen/antibody complexes) [47].

MYOCARDITIS

The clinical spectrum of myocarditis includes: asymptomatic patients who may have electrocardiographic abnormalities, patients with signs of clinical heart failure and ventricular dilatation, and patients with symptoms of fulminant heart failure and severe left ventricular dysfunction without cardiac dilatation [48]. After exclusion of coronary artery disease, clinical presentation of the patients led to the consideration of an acute infectious myocardial process, which is the characteristic indication for endomyocardial biopsy in the search for active myocarditis. Patients in whom myocarditis presented clinically as acute myocardial infarction, active or borderline myocarditis were diagnosed in various percentages. The variation depended on the time interval of biopsy after acute onset of the disease, whereas virus analysis was either not performed or resulted in low evidence of viral genomes.

The association between B19V infection and iCMP (idiopathic cardiomyopathy) has been described recently with the identification of myocardial endothelial cells as target cells of B19V. Furthermore, analyses of consecutive endomyocardial biopsies of patients with progressive left ventricular systolic dysfunction demonstrated the persistence of B19V infection in heart tissue. Besides enteroviruses and human herpesvirus 6, B19V has been described as being the most common agent of biopsy-proven viral myocarditis, which may lead to the development of endothelial cell and isolated left ventricular diastolic dysfunction [49,50].

Viral infections of the heart have become a central issue in studying the pathogenesis of myocarditis and dilated cardiomyopathy. The most common etiologies are infectious agents, hypersensitivity responses, or immune-related injury. However, the etiology might go unrecognized secondary to difficulties in identifying infectious agents. This is particularly truth for viruses in the early stage of infection before the virus is cleared by the immune system. The detection of viral genomes in endomyocardial biopsies by molecular techniques, especially PCR, has greatly expanded the list of viruses implicated in myocarditis: including coxsackieviruses and echoviruses, ADVs, parvovirus B19, human cytomegalovirus, Epstein-Barr-virus, influenza virus A and B, among others [50-54].

Kuethe suggests that B19V demonstrates a lifelong persistence in the heart. The detection of B19V DNA in heart tissue showed no correlation with clinical symptoms. This study analyzed the prevalence of parvoviral DNA in heart tissue obtained from cardiac surgery patients who did not have myocardial diseases that might be associated with viral pathogens (representing the normal adult population and supply further evidence that B19V DNA commonly persists asymptomatically in myocardial tissue) [51].

B19V DNA has also been found in myocardium from healthy heart donors; patients with normal left ventricular function, and in the hearts of patients with amyloidosis or lupus erythematosus, although the number of patients investigated were small. These findings raise the question as to whether B19V really does cause the underlying heart disease or whether it is only an innocent bystander present in the heart as a consequence of an earlier infection, typically occurring during childhood or adolescence.

Moreover, Robert Dennert mentioned that pathogenesis of idiopathic dilated cardiomyopathy (DCM) were characterized by infections with cardiotrophic viruses and immune-mediated responses against the heart. In fact, DCM may be the consequence of immune-mediated inflammatory diseases (IMIDs). He also indicates there aren't previous estimations of whether DCM patients with and without an IMID have different prevalences and quantities of cardiotrophic viruses in the heart. This may suggest that DCM patients with an IMID have a different pathophysiologic mechanism from that which is presented in the virus-induced form of DCM [55].

Recently, C-Thomas Bock et al. [56] reported EMBs of 498 B19V-positive patients. It was a historic cohort study obtained from 38 clinical centers in Germany between 2003 and 2010 for cardiopathological diagnosis of myocarditis and DCM. In addition, 91 uninflamed hearts without cardiac failure served as a control group.

It has been demonstrated that B19V infects endothelial cells of small myocardial blood vessels, which can result in the impairment of myocardial microcirculation, endothelial dysfunction and secondary necrosis of myocardial cells, B19V and the viral proteins of B19V play an important pathophysiological role in modulating inflammatory signaling, regulation of pro-apoptotic processes and modulation of the intracellular Ca2+-activity leading to endothelial dysfunction. Direct damage to fetal myocardial cells by Parvovirus B19 has been reported previously and 15% of all myocardial biopsies obtained from dead fetuses diagnosed with perinatal cariomyopathy were associated with B19 inflammation [30,41].

Recent reports have indicated that coinfection with different cardiotropic viruses of the human heart is common. Human herpes virus 6 (HHV6) has been identified as an important coinfecting pathogen with B19V of the myocardium and resulting in fatal myocarditis in infants. It has been reported that HHV6 is able to transactivate human immunodeficiency virus (HIV) and human cytomegalovirus (HCMV).

It has been shown that parvovirus B19 infection of the myocardium can cause potentially lethal acute myocarditis in infants and adults. Acute B19V infection of endothelial cells is accompanied by the intravascular accumulation, adhesion and penetration of inflammatory cells in to vessel walls, leading to an impairment of the myocardial micro-circulation with secondary myocyte necrosis that can mimic myocardial infarction [52-56].

Acute myocarditis presents multiple challenges in diagnosis and treatment. The pathogenesis is complex and includes direct viral myocardial damage as well as autoimmune reactions against cardiac epitopes. Currently, MRI is an important tool for the diagnosis and follow-up of patients with acute myocarditis and perhaps for the guidance of endomyocardial biopsy [53].

It can be hypothesized that B19V can be reactivated from long-term persistent or latent infection by viral and/or host-specific determinants. B19V-coinfection with other cardiotropic viruses like EV, ADV and HHV6 may contribute to the severity of B19V-myocarditis, possibly by reactivating B19V replication and thereby enhancing virus specific host immune responses, tissue inflammation and the progression to chronic heart failure.

We previously reported a review about B19V [57] in human infections (development of modern therapeutic and prophylactic alternatives as recombinant human parvovirus B19 vaccine.

HIV, tuberculosis, and malaria remain major health challenges in 2013. Globally in 2013, there were 1.8 million new HIV infections, 29.2 million prevalent HIV cases, and 1.3 million HIV deaths. Additionally, malaria cases in the World and deaths grew rapidly from 1990 reaching a peak of 232 million cases (143 million to 387 million) in 2003 and 1.2 million deaths in 2004.

Because of their prominence, there are major UN efforts on an annual basis to track the epidemiology of these three diseases [58].

Severe anaemia is common in Africa. It has a high mortality and particularly affects young children and pregnant women. The prevalence of B19V, malaria and co-infection with B19V and malaria was 4.7%, 41.9% y 2.6% respectively. Microcytic anaemia was associated with B19V and co-infection with B19V and malaria more than normocytic normochromic anaemia. In conclusión, B19V plays a very important role in the aetiology of severe anaemia in persons with mild anaemia. Improving knowledge about B91V has a vital role in the effort to prevent severe anemia in malarial anemia cases [59,60].

Human parvovirus B19-VP1u is known to have a phospholipase A2 motif and its enzyme activity has been associated with various inflammatory processes that may contribute to the activation of macrophages. Tzang et al., suggest the crucial role of sPLA2 activity of B19-VP1u in macrophage activation and may provide clues in understanding the role of B19-VP1u in the host response to B19 infection and B19-related diseases, by increasing migration, phagocytosis, and inflammatory responses such as significant increases of MMP9 activity, IL-6 and IL-1bheta mRNA expression in macrophages.

High levels of proinflammatory cytokines are observed during B19V infection, especially those of IL-1β, gamma interferon, and TNF alpha [17,61].

Knösel has the first report of unusual histomorphology in a lymph node biopsy of a patient with PVB 19 related prolonged fatigue, pancytopenia, and unilateral cervical lymphadenopathy. According to the serological parameters, the PVB19 infection occurred at least some months before admission and renoval of the lymph node. Interestingly, the lymph node pathology, together with the positive detection of PVB19 genome by PCR and immunohistochemical detection of the VP1 and VP2 antigens, revealed a locally persistent infection (mimicking ganglionar tuberculosis) [62].

B19V can mimic several diseases as thrombocytopenic purpura, myelodysplastic syndomes (MDS), leukemic relapse or therapy-induced cytopenia in patients with hematologic malignancies. Delay in proper management B19V can lead to severe complications [63].

B19V and HHV-6 infection, both in children and adults, have reported as mimicking blood and marrow features, and these syndromes spontaneously disappeared in 1-2 months [60,64,65].

The pathogenesis of B19 infection is complex and variable, so it is likely that a combination of mechanisms contributes to the neurologic manifestations, Barah et al. commented on 129 cases, in 89 publications and linked the virus with various neurological aspects either confined to CNS (the most common B19-related neurological cases was encephalic syndromes, representing 38.8% of the total). Intravenous immunoglobulin are considered the only treatment option for many clinical syndromes associated with B19 infection because it is believed that they include a good source of antibodies to neutralize the virus, although the mechanism of IVIG action is not comprehensively known. There were seven deaths following encephalitis associated with B19V, and in 12 cases, long-term neurological sequelae were observed, urging the necessity of rapid diagnosis of B19V infection and swift clinical intervention with combined IVIG and steroid regimen. And recommend that B19V infection should be included in the differential diagnosis of encephalitic syndrome and some PNS manifestations regardless of the age [66].

Knowledge about viral diseases and especially the B19 virus is increasing every day. In the subfamily Parvovirinae of the family Parvoviridae, members of four genera are currently known to infect humans, namely parvovirus B19 (B19V, genus Erythro- parvovirus), human bocavirus (genus Bocaparvovirus), adeno-associated viruses (genus Dependoparvovirus) and human

parvovirus 4 (PARV4, genus Tetraparvovirus). PARV4 was discovered in an intravenous drug user with an acute viral infection syndrome [22,66-69].

In 2005, a newly discovered human parvovirus identified by Allander et al. a human bocavirus was characterized in respiratory secretions of Swedish children and has been associated with lower respiratory tract infections worldwide, often in combination with other viral infections. Related parvoviruses named human bocaviruses 2 to 4 have also been detected in the feces of children with acute flaccid paralysis and diarrhea [22,70].

Also, the transmission for transmission of B19V from the respiratory tract to human bone marrow, along with its infection of the myocardial system, liver system and possibly even more unidentified organs, warrants further investigation [71].

We think the best way to end this article is with the revision of Adeno-associated virus (AAV). A member of the family Parvoviridae that has been widely used as a vector for gene therapy, because of its safety profile, its ability to transduce both dividing and non-dividing cells, and its low immunogenicity. AAV has been detected in many different tissues of several animal species but has not been associated with any disease.

Accumulated evidence gathered over recent decades demonstrated that some members of the Parvoviridae family, in particular the rodent protoparvoviruses (PV) H-1PV, the minute virus of mice and LuIII have natural anticancer activity while being nonpathogenic to humans.

Rodent parvoviruses (PV) are recognized for their intrinsic oncotropism and oncolytic activity, which contribute to their natural oncosuppressive effects. Although PV uptake occurs in most host cells, some of the subsequent steps leading to expression and amplification of the viral genome and production of progeny particles are upregulated in malignantly transformed cells.

Special emphasis will be given to H-1PV that has been evaluated extensively at the preclinical level as an anticancer agent using a number of different *in vitro* and *in vivo* tumor models:

1) Glioma
2) Neuroectodermal tumors
3) Lymphoma
4) Melanoma
5) Mammary carcinoma
6) Pancreatic carcinoma
7) Cervical carcinoma
8) Gastric carcinoma
9) Hepatoma
10) Colon carcinoma

Paglino et al., conclude that LuIII is an important viral candidate meriting further consideration for therapy of malignant glioblastoma and that both the LuIII capsid and NS1 nonstructural protein are critical for maximal effectiveness.

PV-based treatments should pave the way for future clinical testing of anticancer efficacy, after the hoped-for confirmation of H-1PV's safety in the current clinical trial is achieved [72-74].

Oncolytic viruses are gaining momentum as a novel form of anti-cancer therapy.

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