Parvovirus B19 Infection – An Emerging Infectious Disease?

Galia Rahav MD

Department of Clinical Microbiology and Infectious Diseases, Hebrew University-Hadassah Medical School, Jerusalem, Israel

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The development of new and more sophisticated diagnostic techniques has opened up many new avenues of investigation. Using these tools has considerably expanded our knowledge on the infectious etiology of well-established disease states. Recent advances have led us to understand that ulcer disease is a consequence of infection with *Helicobacter pylori*, that Kaposi's sarcoma may be due to infection with human herpesvirus-8, that Whipple's disease is due to a fastidious gram-negative bacillus *Tropherema whippelii*, and that atherosclerosis may be associated with *Chlamydia pneumoniae*. Does parvovirus belong to this list?

The discovery of the human parvovirus B19 in 1975 and the subsequent studies of its effects in humans identified this virus as the causative agent of a broad spectrum of diseases. Recent improvements in the development of sensitive polymerase chain reaction techniques and methods for cultivation have provided new insight into its pathogenic role, its virology and immunology, and the varied clinical manifestations. Parvovirus B19 is a common infectious agent in humans, with a seroprevalence of 50–70% in adults [1]. In normal children parvovirus B19 is known to cause erythema infectiosum (fifth disease). The clinical presentation in normal adults includes fever, malaise, and acute and chronic arthropathy. Transient aplastic crisis can develop in patients with increased erythropoiesis, and pure red cell aplasia develops in immunocompromised patients [1]. Virus-associated hemophagocytic syndrome has also been reported [1]. In pregnant women, the virus can be transmitted to the fetus with an infection rate of about 30%, resulting in fetal anemia, fetal hydrops, miscarriage or intrauterine fetal death [2]. Recently, parvovirus B19 was found to be associated with acute meningoencephalitis [3], brachial plexus neuropathy [4], hepatitis [5], pneumonia [6], myocarditis [7], papular-purpuric gloves and socks syndrome [8] and infection in solid-organ and bone marrow transplanted patients [9]. Acute parvovirus B19 infection has also been implicated in the pathogenesis of several autoimmune or inflammatory conditions including systemic lupus erythematosus [10], rheumatoid arthritis [11], systemic necrotizing vasculitis [12], idiopathic thrombocytopenic purpura [13], acute post-infectious glomerulonephritis [14], Kawasaki disease [15] and multiple sclerosis (1).

In this issue of *IMAJ*, Klar et al. [16] describe an immunodeficient patient with interstitial lung disease – a new clinical manifestation associated with parvovirus B19 infection. Also in this issue, Barash et al. [17] describe 48 children with serologic evidence of acute parvovirus B19 infection; 31 presented with prolonged fever, 6 had unexplained anemia, and 5 had arthritis. In six patients each had an unusual presentation, including SLE, leukocytoclastic vasculitis, Diamond-Blackfan syndrome, hepatitis, optic neuritis, and acute lymphoblastic leukemia.

However, most of the publications cited above are case reports associated with the virus, or limited PCR-based studies with poorly documented controls. Not only does the broad spectrum of clinical presentations attributed to parvovirus B19 not fit the very narrow target cell range of the virus, but parvovirus B19 apparently can be propagated only in human erythroid cells. Susceptibility to parvovirus B19 increases with differentiation, the pluripotent stem cell appears to be spared, and the main target cells are erythroid progenitors. Erythroid specificity of parvovirus B19 results from the tissue distribution of the virus' cellular receptor, globoside, also known as blood group P antigen, which is found in erythroid progenitors, erythroblasts and megakaryocytes [18]. It is also present in endothelial cells, which may be targets of viral infection involved in the pathogenesis of transplacental transmission, possibly vasculitis, and the rash of fifth disease. Rare individuals who genetically lack P antigen in erythrocytes are resistant to parvovirus B19 infection, and their bone marrow cannot be infected with parvovirus B19 *in vitro*. Erythroid specificity may also be modulated by specific erythroid cell transcription factors. The rash and polyarthropathy are probably immune complex-mediated. However, *in vitro* studies have shown that the parvovirus B19 non-structural protein, in addition to inducing apoptosis in host cells, also induces activation of interleukin 6 [19], which could contribute *in vivo* to the parvovirus B19-induced arthropathy and/or autoimmune antibody production.

The laboratory diagnosis of parvovirus B19 infection is not trivial. The virus cannot easily be cultivated in the laboratory, and the detection of virus relies on DNA hybridization techniques. In immunocompetent patients, viral DNA can be detected in the serum only within 2–4 days, and the diagnosis of acute cases is therefore based on immunoglobulin M assays. However, serologic confirmation of any viral infection cannot be made with a single serum sample, as was performed by Barash et al. [17]. Serologic tests for antiviral antibody are, at best, imperfect and subject to

SLE = systemic lupus erythematosus

many potential errors. These can only be handled with adequately cautious and informed interpretation. One of the common problems seen today and one of great importance for public health surveillance and epidemic detection is false positivity in IgM antibody detection. In almost all tests for IgM antibody to virtually all viruses, if enough samples are tested some of them will turn up as false positives. Ideally, IgM testing is performed by the capture technique. In a radioimmunoassay or enzyme-linked immunosorbent assay format, IgM can be detected in more than 90% of cases by the third day of aplastic crisis or at the time of rash in erythema infectiosum. IgM antibody remains detectable for 2 to 3 months after infection. Parvovirus B19 IgG can be detected by capture assay or indirect assay, and is usually present by the seventh day of illness and probably for life thereafter [20]. Recent infection can be confirmed by IgG avidity studies. In immunocompetent individuals, the early antibody response is to the major capsid protein VP2, but as the immune response matures the reactivity to the minor capsid protein VP1 dominates. Sera from patients with persistent parvovirus B19 infection typically contain antibody to VP2 but not to VP1 [21]. In contrast to patients with erythema infectiosum, those with transient aplastic crisis are often viremic at the time of presentation; therefore, the diagnosis is readily made by detection of parvovirus B19 DNA in the serum. The use of PCR techniques has greatly increased the sensitivity level of detection of parvovirus B19, at the risk of possible contamination and false positive results that confuse interpretation. Even in immunocompetent persons, parvovirus B19 DNA may be detectable in serum by PCR for more than 4 months after acute infection [22] and for years in bone marrow, synovial tissue, and liver [23], suggesting persistence of the virus in the body. Because of the presence of PCR-detectable parvovirus B19 DNA in healthy persons, the detection of parvovirus B19 in serum, bone marrow or synovial fluid may not confirm the diagnosis [24]. A real-time PCR assay for quantitative detection of parvovirus B19 DNA in clinical serum samples, carried out using a light cycler, was found to be sensitive, specific and rapid [25].

In conclusion, parvovirus B19 infection is a new, emerging infectious disease that has also been implicated in the pathogenesis of several autoimmune or inflammatory conditions. The laboratory diagnosis of parvovirus B19 is problematic due to false positive IgM and the presence of PCR-detectable B19 DNA in healthy persons. Given the availability of effective therapy with intravenous IgG for severe disease and of intrauterine blood transfusions for hydrops in the fetus, the development of better techniques for diagnosis is imperative.

References

1. Brown K. Parvovirus B19. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. 5th edn. Philadelphia: Churchill Livingstone, 2000:1685–93.
2. Anand A, Gray ES, Brown T, Clewley JP, Cohen BJ. Human parvovirus infection in pregnancy and hydrops fetalis. *N Engl J Med* 1987;316(4): 183–6.
3. Barah F, Vallely PJ, Chiswick ML, Cleator GM, Kerr JR. Association of human parvovirus B19 infection with acute meningoencephalitis. *Lancet* 2001;358:729–30.
4. Walsh KJ, Armstrong RD, Turner AM. Brachial plexus neuropathy associated with human parvovirus infection. *Br Med J* 1988;296:896.
5. Yoto Y, Kudoh T, Haseyama K, Suzuki N, Chiba S. Human parvovirus B19 infection associated with acute hepatitis. *Lancet* 1996;347:868–9.
6. Janner D, Bork J, Baum M, Chinnock R. Severe pneumonia after heart transplantation as a result of human parvovirus B19. *J Heart Lung Transplant* 1994;13(2):336–8.
7. Enders G, Dotsch J, Bauer J, et al. Life-threatening parvovirus B19-associated myocarditis and cardiac transplantation as possible therapy: two case reports. *Clin Infect Dis* 1998;26(2):355–8.
8. Passoni LF, Ribeiro SR, Giordani ML, Menezes JA, Nascimento JP. Papular-purpuric "gloves and socks" syndrome due to parvovirus B19: report of a case with unusual features. *Rev Inst Med Trop Sao Paulo* 2001;43(3):167–70.
9. Broliden K. Parvovirus B19 infection in pediatric solid-organ and bone marrow transplantation. *Pediatr Transplant* 2001;5(5):320–30.
10. Diaz F, Collazos J, Mendoza F, et al. Systemic lupus erythematosus associated with acute parvovirus B19 infection. *Clin Microbiol Infect* 2002;8(2):115–17.
11. Kerr JR, Cartron JP, Curran MD, Moore JE, Elliott JR, Mollan RA. A study of the role of parvovirus B19 in rheumatoid arthritis. *Br J Rheumatol* 1995;34(9):809–13.
12. Leruez-Ville M, Lauge A, Morinet F, Guillevin L, Deny P. Polyarteritis nodosa and parvovirus B19. *Lancet* 1994;344:263–4.
13. Heegaard ED, Rosthoj S, Petersen BL, et al. Role of parvovirus B19 infection in childhood idiopathic thrombocytopenic purpura. *Acta Paediatr* 1999;88(6):614–17.
14. Takeda S, Takaeda C, Takazakura E, Haratake J. Renal involvement induced by human parvovirus B19 infection. *Nephron* 2001;89(3):280–5.
15. Cohen BJ. Human parvovirus B19 infection in Kawasaki disease. *Lancet* 1994;344:59.
16. Klar A, Halamish A, Shoseyov D, et al. Chronic human parvovirus B19 infection associated with interstitial lung disease. *IMAJ* 2002;4:825–6.
17. Barash J, Dushnitzky D, Sthoeger D, Bardenstein R, Barak Y. Human parvovirus B19 infection in children: uncommon clinical presentations. *IMAJ* 2002;4:763–5.
18. Brown KE, Anderson SM, Young NS. Erythrocyte P antigen: cellular receptor for B19 parvovirus. *Science* 1993;262:114–17.
19. Moffatt S, Tanaka N, Tada K, et al. A cytotoxic nonstructural protein, NS1, of human parvovirus B19 induces activation of interleukin-6 gene expression. *J Virol* 1996;70(12):8485–91.
20. Tolfvenstam T, Ruden U, Broliden K. Evaluation of serological assays for identification of parvovirus B19 immunoglobulin M. *Clin Diagn Lab Immunol* 1996;3(2):147–50.
21. Kurtzman GJ, Cohen BJ, Field AM, Oseas R, Blaese RM, Young NS. Immune response to B19 parvovirus and an antibody defect in persistent viral infection. *J Clin Invest* 1989;84(4):1114–23.
22. Patou G, Pillay D, Myint S, Pattison J. Characterization of a nested polymerase chain reaction assay for detection of parvovirus B19. *J Clin Microbiol* 1993;31(3):540–6.
23. Cassinotti P, Burtonboy G, Fopp M, Siegl G. Evidence for persistence of human parvovirus B19 DNA in bone marrow. *J Med Virol* 1997;53(3):229–32.
24. Eis-Hubinger AM, Reber U, Abdul-Nour T, Glatzel U, Lauschke H, Putz U. Evidence for persistence of parvovirus B19 DNA in livers of adults. *J Med Virol* 2001;65(2):395–401.
25. Manaresi E, Gallinella G, Zuffi E, Bonvicini F, Zerbini M, Musiani M. Diagnosis and quantitative evaluation of parvovirus B19 infections by real-time PCR in the clinical laboratory. *J Med Virol* 2002;s67(2):275–81.

Correspondence: Dr. G. Rahav, Dept. of Clinical Microbiology and Infectious Diseases, Hebrew University-Hadassah Medical School, P.O. Box 12000, Jerusalem 91120, Israel.
Phone: (972-2) 677-6594. Fax: (972-2) 641-9545
email: rahavg@md2.huji.ac.il.

Ig = immunoglobulin
PCR = polymerase chain reaction