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CASE REPORT

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Intravenous immunoglobulin therapy for severe arthritis associated with human parvovirus B19 infection

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Abstract Symptoms caused by acute human parvovirus B19 (HPV-B19) infection can vary considerably, from asymptomatic to severely symptomatic. A 39-year-old Japanese woman complained of sudden, severe arthralgia with edematous limbs coincident with an outbreak of HPV-B19 infection at the elementary school attended by her daughter. A diagnosis of acute HPV-B19 infection was made by the detection of serum antibody to HPV-B19 IgM and HPV-B19 DNA. Magnetic resonance imaging revealed bilateral synovitis of the cubital joints. The patient was immunocompetent and suffered from severe arthralgia associated with persistent HPV-B19 viremia for more than 4 months after the diagnosis of acute HPV-B19 infection. The administration of high-dose intravenous immunoglobulin resulted in remission, with little change in the serum HPV-B19 DNA level. Even in our immunocompetent patient, severe and prolonged arthritis was found to be associated with persistent viremia.

Key words Human parvovirus B19 · Synovitis · Arthritis · Immunoglobulin therapy

Introduction

Parvovirus B19, the only known human pathogenic parvovirus, is a small, non-enveloped, single-stranded DNA virus classified in the *Erythrovirus* genus of the Parvoviridae family. Human parvovirus B19 (HPV-B19) has a wide variety of disease manifestations dependent on the immunological and hematological status of the host. HPV-B19 DNA has been found in the respiratory secretions of patients at the time of viremia,[1] suggesting that infection is generally spread by a respiratory route. Transmission is most likely to occur among individuals in a household, in daycare, or in crowded environments. This scenario places women with young children at high risk for acquiring infection.

The virus is the cause of various diseases including erythema infectiosum (EI), also called fifth disease or slapped cheek disease, polyarthropathy, fetal hydrops, chronic fatigue syndrome, transient aplastic crisis, pure red cell aplasia (PRCA), and chronic anemia.[2] In normal immunocompetent children, HPV-B19 is the cause of EI. Especially in immunocompetent women, an acute symptomatic polyarthropathy that can mimic rheumatoid arthritis occurs occasionally. In an immunocompromised host, persistent HPV-B19 viremia manifests as PRCA and chronic anemia.

We report the case of an immunocompetent Japanese adult woman with persistent HPV-B19 viremia who developed chronic severe HPV-B19-associated arthritis without PRCA or chronic anemia and who experienced remission from the disease after receiving high-dose intravenous immunoglobulin (IVIg) therapy.

Case report

On 20 December 2005 (day 1), a 39-year-old Japanese woman complained of severe arthralgia with edematous limbs, leading to a feeling of severe fatigue. Her symptoms occurred suddenly and were coincident with an outbreak of HPV-B19 infection at the elementary school attended by her daughter. Her prodromal symptoms did not include low-grade fever, chill, rash on the face, itching, upper respiratory tract complains, cough, nausea, or diarrhea. One week after the onset (27 December, day 8), an aggravation of the symptoms was seen, and she was not able to rise from a lying posture because of severe pain of the extremities. She was transported by ambulance and admitted to our

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hospital. She had apparently been immunocompetent until that time. She did not have a family history of rheumatoid arthritis (RA) or collagen disease, but did have contact with a juvenile patient with fifth disease on 2 December 2005 (day –18).

On admission, physical examination showed her consciousness level to be alert, height 154 cm, body weight 46 kg, body temperature 37.1°C; blood pressure 126/76 mmHg, and pulse rate 56/min and regular. There was no anemia, jaundice, conjunctivitis, pharyngitis, tonsillitis, or rash. Edematous lesions of the lower extremities were found. Swelling of the bilateral interphalangeal and elbow joints was also seen. There was no warmth, erythema, trauma, subluxation, dislocation, or deformity of the joints. For reasons of intense pain, the range of motion of the cervical vertebrae and bilateral interphalangeal, wrist, cubital, shoulder, knee, and ankle joints was limited. The range of left cubital joint flexion was only 10 degrees and that of the right was 20 degrees, with bilateral knee joint flexion only 20 degrees. No other neurological symptoms were found. Heart and respiratory sounds were normal, and abdominal examination revealed no hepatomegaly or splenomegaly.

On admission, laboratory data (Table 1) showed white blood cell count to be 8060/μl (neutrophils 82.5%, lymphocytes 14.3%, monocytes 2.6%), red blood cell count 459×10^4/μl, hemoglobin 11.9 g/dl, reticulocyte count 4.2×10^4/μl, and platelet count 38.9×10^4/μl, suggesting a slight decrease in hemoglobin but no absence of an increase in reticulocytes or a decrease in neutrophil, lymphocyte, or platelet count. Bone marrow examination revealed that the tissue was normocellular and that the three hematopoietic series, including erythroid series, were well preserved. Inflammatory markers such as C-reactive protein (CRP, 0.13 mg/dl) and erythrocyte sedimentation rate (ESR, 27 mm/h) were slightly increased. Serum uric acid, liver biochemical test values, and immunoglobulin levels in serum were not elevated. Tests for serum antibody to human immunodeficiency virus (HIV) and HIV RNA were negative. Serum rheumatoid factor (RF) [antibodies to immunoglobulin G (IgG)], antibody to streptolysin O (ASO) and antibody to cyclic citrullinated peptide antibody (anti-CCP) were all negative, as were other serological tests for collagen diseases, except for antinuclear antibodies (ANA) and antibody to cardiolipin antibodies (anti-CL). The patient was found to be positive for serum antibody to HPV-B19 (anti-HPV-B19) immunoglobulin M (IgM) in serum at a level of 9.37 IU/ml by enzyme-linked immunoassay (ELISA) and anti-HPV-B19 IgG in serum at a level of 9.26 IU/ml by ELISA (the reference ranges for a positive result are both over 0.80 IU/ml); therefore, she was diagnosed with acute HPV-B19 infection. Serum HPV-B19 DNA level was determined by real-time polymerase chain reaction (PCR) using a commercial kit (Roche Diagnostic, Mannheim, Germany), and the level on admission was 4.2 logarithmic transformed genome equivalents (log gEq)/ml. Magnetic resonance imaging (MRI) revealed synovitis of the left cubital joint, although the wrists and elbows showed no erosive or degenerative changes on 28 December 2005 (day 9) (Fig. 1A). Bone scintigraphy revealed focal areas of increased uptake in the overall joints, especially for the left shoulder and the left cubital joints (Fig. 2); therefore, she was diagnosed with arthritis associated with acute HPV-B19 infection. Synovial fluid aspiration and analysis were not performed.

The clinical course of the patient is shown in Fig. 3. Initially she was treated with a nonsteroidal antiinflammatory drug (NSAID). Although she was able to get out of bed by herself (day 15) and was able to walk with crutches (day 30), she suddenly suffered a recurrence of severe fatigue and arthralgia of the elbows, knees, back, neck, fingers, and wrists and could not rise from the bed by herself on 8 March 2006 (day 79). Most of her daily living activities were markedly curtailed by this disease. The findings of routine laboratory tests were still normal. Serological investigation continued to show her to be negative for RF and anti-CCP antibody; furthermore, ANA and anti-CL became negative at baseline, but the serum HPV-B19 DNA level fluctuated from 4.2, to 3.2, and to 3.6 log gEq/ml, and her symptoms developed to a more severe status. The NSAID treatment was not able to control her arthralgia. On 25 April 2006 (day 127), to eliminate the HPV-B19 viremia from circula-

Table 1. Laboratory data on admission (27 Dec 2005)

Hematology		**Biochemistry**		**Immunology**	
WBC	8060/μl	TP	7.7 g/dl	CRP	0.13 mg/dl
Neut.	82.5%	Alb	4.3 g/dl	CH-50	44 IU/ml
Lym.	14.3%	BUN	10 mg/dl	C3	141 mg/dl
Mono.	2.6%	Cr	0.51 mg/dl	C4	26 mg/dl
Eos.	0.1%	UA	3.1 mg/dl	ASO	142 IU/ml
RBC	459×10^4/μl	Na	146 mmol/l	ANA	40 titer
Reti	4.2×10^4/μl	K	4.6 mmol/l	Anti-CL	31 IU/ml
Hb	11.9 g/dl	Cl	104 mmol/l	RF	< 5 IU/ml
Ht	38.6%	AST	22 IU/l	MMP-3	17.3 ng/ml
Plt	38.9×10^4/μl	ALT	25 IU/l	Anti-CCP	<0.6 IU/ml
		LDH	200 IU/l		
		ALP	212 IU/l	**Infection**	
		γ-GTP	20 IU/l	Anti-HIV-1	(–)
				HBs Ag	(–)
				Anti-HCV	(–)
Urine				HPV-B19 IgM	9.37 IU/ml
Prot	(–)	**ESR**		HPV-B19 IgG	9.26 IU/ml
OB	(–)	27 mm/h		HPV-B19 DNA	4.2 log gEq/ml