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Human parvovirus B19 infection mimicking systemic lupus erythematosus

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Abstract Although several recent reports have discussed the similarities between human parvovirus B19 (HPV-B19) infection and systemic lupus erythematosus (SLE), the relationship between these conditions has not been established owing to the small number of patients investigated. In 1998–1999, an outbreak of *Erythema infectiosum* occurred close to our hospital, enabling us to investigate the clinical, hematological, and serological findings, including serum complement and antinuclear antibodies (ANA), in 22 patients with acute HPV-B19 infection. The principal symptoms included rash (86.3%), edema (59%), arthralgia (45.4%) and fever (31.8%). Lymphadenopathy was seen in three of the 22 cases. The laboratory findings showed high incidences of leukopenia (50%), hypocomplementemia (95%), and ANA (64.7%). At the time of disease onset, patients with acute HPV-B19 infection presented with features which were similar to those of SLE. The possibility of HPV-B19 infection should therefore be considered in patients presenting with SLE-like features.

Key words Antinuclear antibodies · Hypocomplementemia · Parvovirus B19 · Systemic lupus erythematosus (SLE)

Introduction

Human parvovirus B19 (HPV-B19) is a small virus consisting of single-strand DNA.[1] It has been associated with a variety of clinical syndromes, including aplastic crisis in chronic hemolytic anemia,[2] and intrauterine infection with *Hydrops fetalis*.[3] The most common disease caused by HPV-B19 is *Erythema infectiosum* (fifth disease),[4] which occurs primarily in children (the so-called "slapped cheek syndrome"). In adults, HPV-B19 has been associated with arthropathies, and several case reports have documented the association between HPV-B19 infection and rheumatic disease.[5–10] Recently, several reports have discussed the similarities between HPV-B19 infection and systemic lupus erythematosus (SLE).[11–16] Although these reports described striking similarities between the clinical, hematological, and serological features of SLE and HPV-B19 infection, the number of patients in each series was small and some reports were reviews of the literature. From the winter of 1998 to the summer of 1999, an epidemic of *Erythema infectiosum* in children occurred at Nagaoka, Japan, and the surrounding area. At that time, many adult patients visited our hospital with eruptions and arthropathies, and their clinical features and laboratory findings were strikingly similar to those of SLE. We investigated the clinical and serological characteristics of 22 subjects with acute HPV-B19 infection.

Materials and methods

From January 1998 through August 1999, 31 patients were diagnosed at the Nagaoka Red Cross Hospital as having acute HPV-B19 infection because their sera were positive for anti-HPV-B19 IgM antibodies. For 22 patients, hematological and serological findings were available in addition to the results of anti-HPV-B19 antibody tests. The clinical features and laboratory data of the 22 patients were examined retrospectively. There were 19 women and 3 men, aged between 15 and 43 years (mean age 31.6 years). Nineteen patients had previously been healthy. One female patient had leukopenia with low serum C3 levels and was positive for antinuclear antibody before her HPV-B19 infection, and had been followed up as possibly having SLE. One female

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patient had systemic sclerosis and was being treated with D-penicillamine. One man had been admitted for the treatment of diabetes insipidus. Anti-HPV-B19 IgM antibody and complete blood cell counts (CBC) were examined in all patients. Some of the sera were tested for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor, liver function, serum complements (C3, C4, CH50), antinuclear antibodies (ANA), and anti-DNA, anti-Sm, and anti-RNP antibodies. ANA was tested with an ANA/HEp-2 test kit based on the indirect immunofluorescent antibody technique.

Results

Clinical features (Table 1)

Sixteen patients (cases 1–16) presented at the Department of Internal Medicine, and the others (cases 17–22) presented at the Department of Dermatology. Some of them were referred to us from peripheral medical centers as having rheumatic disease. The onset of symptoms occurred throughout the year without any seasonal or monthly pattern. The chief subjective symptoms were rash (86.3%), edema (59%), arthralgia (45.4%), and fever (31.8%). Rashes were observed mainly on the arms and legs and disappeared immediately, or within a few days. Although "slapped cheek syndrome" is characteristic in *Erythema infectiosum*, few patients showed a facial rash in our study. Malar rash and discoid rash were not seen in any patient. Three patients presented without any rash. Edema was shown in 13 patients, mainly in the fingers, legs, and/or face, and all patients complained of stiffness. Arthralgia and/or arthritis occurred in 10 patients. This was usually symmetrical and most commonly affected the joints of the hands, wrists, and knees. In many cases, the arthralgia improved within a few days or weeks, but in one female patient it persisted for 6 months (case 3). Seven patients had transient fevers. Lymphadenopathy occurred in three patients. Oral ulcers, photosensitivity, serositis, and neurological disorders were not observed in any patient. Nine patients, including four members of the medical staff, had a history of contact with individuals with *Erythema infectiosum*.

Laboratory findings (Table 2)

All patients were positive for IgM antibodies to HPV-B19. Leukopenia (WBC $< 4000/mm^3$) was observed in 11 of 22 patients (50%) at the time of first examination. Ten patients were followed-up for leukopenia after a few weeks, and the leukopenia had improved in all of them. Anemia was noted in a few cases, but no decrease in reticulocytes was observed. Thrombocytopenia was not observed in any patient. Liver enzymes were elevated in a few cases. No abnormalities in urinalysis were observed. ESR was elevated in some cases but CRP was not. No patient was positive for rheumatoid factor. Hypocomplementemia was observed in most of the patients. Low C3 levels were observed in 14/20 (70%)

Table 1. Clinical manifestations in patients with HPV-B19 infection

Patient No.	Age (years)/ sex	Underlying disease	Onset	Rash	Edema	Arthralgia/ arthritis	Fever	Other	Source of exposure
1	33/F	SLE suspected	Feb. 98	F,A&L				LN swelling	Hospital (dermatologist)
2	31/F	None	Apr. 98	A&L		(+)			Children
3	41/F	None	Jan. 99	(–)	Fingers				Hospital (nurse)
4	38/F	Scleroderma	Jun. 98	A&L	Fingers	(+)			Children
5	43/F	None	Jan. 98	(–)	Fingers, legs			LN swelling	Unknown
6	38/F	None	Nov. 98	A&L	Fingers				Children (case 7)
7	15/F	None	Nov. 98	A&L					Unknown
8	24/F	None	May 99	A&L		(+)	(+)		Unknown
9	57/F	Anemia	Jun. 98	A&L	Face, fingers				Unknown
10	19/F	None	Sep. 98	F	Fingers	(+)			Unknown
11	21/F	None	Mar. 99	A&L	Fingers	(+)			Children (nursery nurse)
12	32/F	None	Apr. 99	A&L	Fingers, legs	(+)			Unknown
13	36/F	None	Mar. 99	A&L	Fingers				Children
14	19/F	None	Aug. 99	A&L		(+)			Unknown
15	36/F	None	Aug. 99	(–)	Face, fingers	(+)	(+)		Unknown
16	35/F	Asthma	May 99	A&L			(+)	LN swelling	Unknown
17	19/M	Diabetes insipidus	Mar. 98	F,A&L			(+)		Unknown (on admission)
18	41/F	None	Aug. 98	F,A&L	Face		(+)		Unknown
19	26/M	None	Jun. 98	A	Face		(+)		Unknown
20	33/F	None	Jun. 98	A&L	Fingers	(+)			Unknown
21	28/M	None	May 99	A&L			(+)		Children, wife (case 22)
22	31/F	None	May 99	A		(+)		Headache	Hospital (nurse)

A, arms; L, legs; F, face; LN, lymph nodes

Table 2. Laboratory data in patients with HPV-B19 infection

Case	Age (years)/ sex	B19 IgM ($N < 0.8$)	WBC (/mm^3)	Hb (g/dl)	Ret ($\times 10^9$/l)	PI (/mm^3)	GOT (IU/l)	GPT (IU/l)	LDH (IU/l)	Urinalysis U-Pr/OB	ESR (mm/h)	CRP (mg/dl)	C3 (mg/dl) (N 75–150)	C4 (mg/dl) (N 15–40)	CH50 (U/l) (N 25–50)	ANA ($\times$)
1	33/F	8.87	1900	12.1	1	18.2	63	42	202	−/−	19	<0.2	27	3	14	80 (PCNA)
2	31/F	5.96	5400	12.5	ND	17.4	21	20	210	−/−	8	ND	46	16	32	40 (sp)
3	41/F	25.96	4000	11.2	ND	30.3	24	32	258	−/−	29	0.3	37	10	17.1	40 (sp)
4	38/F	11.78	7800	9.9	ND	27.1	26	49	174	−/−	28	<0.2	88	13	28.1	640
5	43/F	9.81	3500	11.5	ND	20.4	34	23	233	−/−	29	<0.2	32	8	18	(–)
6	38/F	10.31	4200	13.1	ND	20.3	22	23	207	−/−	27	0.3	40	9	11.9	(–)
7	15/F	11.13	3200	12.2	ND	26.3	19	19	144	−/−	23	0.3	54	8	ND	320 (homo)
8	24/F	10.17	1900	12.6	ND	12.8	17	27	222	ND	ND	ND	ND	ND	ND	80 (homo)
9	57/F	11.26	3800	12	ND	31.8	15	20	210	ND	ND	ND	66	11	34.6	ND
10	19/F	12.49	3500	12.4	ND	20.9	110	150	287	−/−	18	ND	53	10	24.4	(–)
11	21/F	5.87	3400	12.2	ND	19.6	21	33	180	−/−	ND	ND	63	6	15.7	40 (homo)
12	32/F	11.57	3900	12	ND	21.4	39	51	254	+−/−	ND	<0.3	46	8	18.1	(–)
13	36/F	10.2	6400	13.2	ND	27.5	20	20	216	ND	ND	<0.2	60	11	24.8	80 (homo)
14	19/F	10.81	5100	12.7	ND	22.5	32	29	230	−/+−	45	0.5	76	17	<10	(–)
15	36/F	0.82	4300	12.3	ND	30.7	14	12	226	−/−	ND	ND	76	9	26.6	80 (sp)
16	35/F	10.94	5000	11.3	10	26.9	35	34	246	−/−	ND	<0.2	ND	ND	ND	ND
17	19/M	10.25	7400	9.4	25	25.2	30	65	178	−/−	22	0.4	47	9	14	(–)
18	41/F	8.92	3000	14	10	12.7	33	35	258	ND	ND	<0.2	63	19	ND	560 (dis–sp)
19	26/M	4.65	6400	15.4	27	26.1	22	30	225	−/−	ND	ND	121	26	ND	ND
20	33/F	12.42	5500	11.7	10	27.3	11	18	161	−/−	28	ND	89	12	ND	ND
21	28/M	11.86	2500	14	2	11.7	22	36	234	ND	ND	0.3	93	12	ND	160 (homo)
22	31/F	4.29	7900	11.2	1	21.7	14	21	210	ND	ND	0.5	62	7	23.5	ND

Ret, reticulocyte count; ND, not determined; U-Pr, urine protein; OB, occult blood; sp, speckled; homo, homogenous; dis–sp, discrete–speckled; LDH, lactic dehydrogenase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ANA, antinuclear antibodies; PCNA, proliferating-cell nuclear antigen

patients, and low C4 in 16/20 (80%). CH50 levels were also low in 10/15 (66.7%) cases. In total, hypocomplementemia was observed in 95% of the patients (19/20). Eleven patients were reexamined for complement levels a few weeks later, and in all cases the hypocomplementemia had improved. ANA were present in 11/17 cases (64.7%), but no patients had anti-dsDNA antibodies or anti-Sm antibodies. In two women who were positive for ANA before the HPV-B19 infection (case 1 was probably SLE; case 4 was systemic sclerosis), ANA positivity persisted after the remission of the HPV-B19 infection. In one patient (case 2), ANA was negative at the 6-month follow-up, but three patients showed ANA positivity at the 4- to 16-week follow-ups. Five patients were not followed up for ANA. The relationship between symptoms and laboratory abnormalities was unclear because most of the patients had a rash, arthralgia, and edema. Although the clinical and laboratory findings of patients with HBV-B19 were similar to those of patients with SLE, none of the patients showed the criteria for classification of SLE in 1982.

Case presentation

Case 1

A 33-year-old woman (a dermatologist) had been identified as having leukopenia when she was 20 years old. In December 1997, her blood test results were as follows: leukocyte count, 3900/mm^3; ANA, positive (1:640, PCNA pattern); antibodies to dsDNA, SS-A, SS-B, Sm, RNP, and Scl-70, negative. Her C3 was low (44 mg/dl), but her C4 and CH50 were within the normal ranges. She had no symptoms and had been followed up as possibly having SLE, but she had no therapy. In February 1998, she developed a rash involving the face, arms, and legs. Her WBC was 1900/mm^3, her platelet count was 18.2×10^4/mm^3, her ANA was positive (1:80, PCNA pattern), and her levels of complements were markedly low (C3 27 mg/dl, C4 3 mg/dl, CH50 14 U/l). Because antibodies to HPV-B19 were present for IgM, she was diagnosed as having acute HPV-B19 infection rather than an exacerbation of SLE. The skin rash disappeared in a few days, and her WBC and complement levels gradually increased. In March 1998, her WBC was 3900/mm^3, her C3 was 38 mg/dl, her C4 was 17 mg/dl, and her CH50 was 34 U/l. In May 1998, her blood test results returned to the levels observed before she acquired the HPV-B19 infection.

Discussion

HPV-B19 infection has been associated with a number of clinical conditions. In a clinicoepidemiological study of an outbreak of HPV-B19 infection at a junior school, Woolf et al.[7] investigated the clinical manifestations of the infection closely. These authors identified acute arthropathy as the most marked clinical manifestation in adults, which agrees with other reports of HPV-B19 infections in the literature. Some authors have reported that HPV-B19 may trigger a transient autoimmune state,[17,18] and several studies have documented the association between HPV-B19 infection and rheumatic disease.[5–10] Recently, several reports have discussed the similarities between HPV-B19 infection and SLE.[11–16] Nesher et al.[12] reported four cases of HPV-B19 infection in adults which mimicked SLE, and reviewed 10 other reported cases. In both diseases, malar rash, fever, arthropathy, myalgia, cytopenia, hypocomplementemia, and ANA can be observed, and the authors pointed out these similarities. In 1999, Trapani et al.[13] reported four pediatric patients with a "lupus-like" syndrome that correlated with HPV-B19 infection, and compared the clinical and laboratory findings of these patients with SLE features and HPV-B19 infections reported in the literature. Moore et al.[11] also described seven patients with findings suggestive of SLE, but later diagnosed as HPV-B19 infection. Although these reports showed striking similarities between the clinical, hematological, and serological features of SLE and HPV-B19 infection, it is unclear whether these similarities are common.

In our study, a high incidence of leukopenia, hypocomplementemia, and ANA was observed in patients during an outbreak of acute HPV-B19 infection. The inhibition of erythropoiesis with reticulocytopenia is particularly well documented in HPV-B19 infection,[2,11–13] although none of our patients presented with marked anemia or reticulocytopenia.

Although hypocomplementemia and ANA positivity is well documented in HPV-B19 infection, their frequency varies between patients. White et al.[6] observed low C4 in seven and high C3 in three of 19 patients with parvovirus-associated arthropathy. Fawaz-Estrup[14] investigated the clinical and serological features of nine adult patients with HPV-B19 infection who presented with polyarthralgias/polyarthritis. In that study, low C3 levels were observed in 1/6 cases, low C4 in 2/6 cases, and elevated ANA in 4/9 cases. One patient developed SLE. Three women had angioedema; one also had transient C1 esterase inhibitor deficiency, and another a transient decrease in C4 levels. Fawaz-Estrup described the parvovirus infection as having a spectrum of clinical manifestations, including angioedema and the presence of autoantibodies, and low C4 and C1 esterase inhibitor concentrations which mimicked SLE. Soloninka et al.[18] reported that 68% of individuals recently recovered from HPV-B19 infection had elevated levels of anti-dsDNA and anti-ssDNA antibodies. Garcia-Tapia et al.[19] evaluated the clinical and hematological findings in 43 patients with HPV-B19 infection and found hematological abnormalities in 13.9%, arthralgia/arthritis in 20.9%, and circulating immune complexes in 81.6%. Gendi et al.[20] examined 47 patients with proven HPV-B19 infection during an outbreak in Oxfordshire (UK) in 1993, and looked at C3 and C4 complement components and ANA 1 year later. Decreased C4 levels were observed in four patients, and an ANA titre of 40 was present in two cases. C3 levels were normal in all patients. There was no correlation with symptoms. In 1987–1988, in the Sendai area, Sasaki et al.[17] examined 19 adult patients with acute HPV-B19 infection for the

presence of ANA and rheumatoid factor. Among these, four were positive for ANA and four were positive for rheumatoid factor.

Because our study was uncontrolled, the precise frequency of hypocomplementemia and ANA positivity during outbreaks of HPV-B19 infection has not been established. As many of our patients had a presentation which was compatible with rheumatic disease, particularly those who presented at the Department of Internal Medicine, it is possible that a selection bias might have been introduced in this study. There is also a possibility that there may be regional differences in the features. However, it seems likely that a considerable number of patients with HPV-B19 infection, particularly adults, present with hypocomplementemia and positive ANA. A controlled study is required to determine the hematological and immunological features of outbreaks of HPV-B19 infection.

Although HPV-B19 infection closely resembles SLE at the time of disease onset, the clinical course is different. In most cases, clinical findings and serological abnormalities normalized within a few weeks in HPV-B19 infection without any treatment. The course is usually self-limited, although symptoms may be prolonged for up to several months in certain individuals.[7,11–16] In our study, the clinical symptoms had improved after a few weeks in all but one patient, in whom arthralgia persisted for 6 months. The leukocytopenia and hypocomplementemia were also self-limited. The serum complement levels were higher in all cases after a few weeks. On the other hand, ANA positivity seemed to persist longer than hypocomplementemia. In our study, ANA positivity persisted in four patients for 1–4 months. In only one patient did ANA titers return to normal after 6 months. In most cases described in the literature, the ANA positivity associated with HPV-B19 infection became negative after several weeks to several months, but in some patients it persisted for longer than a year.[11–16,21–24]

As described above, the clinical and serological abnormalities in HPV-B19 infection were transient in most cases, but in some cases they persisted longer, and treatment was required. Cases of concurrent HPV-B19 infection and SLE[22–24] suggest that a parvovirus may play a role in the pathogenesis of SLE. However, no serological results were available before the onset of illness in most cases, and therefore it remains unclear whether parvovirus infection might lead to the development or exacerbation of SLE. In our study, one female patient (case 1 in the case presentation) who had leukopenia, low serum C3 levels, and was positive for ANA before HPV-B19 infection did not develop SLE after HPV-B19 infection. The patient with scleroderma, who had been treated with D-penicillamine and had positive ANA, also did not develop SLE.

In summary, the similarities to SLE were shown widely in patients with acute HPV-B19 infection at the time of disease onset. The possibility of HPV-B19 infection should be considered in patients presenting SLE-like features, especially in cases with arthralgia and/or edema, or a self-limiting disease course. It is important to ask patients about contacts with individuals who have had *Erythema infectiosum*, and to conduct serological tests for HPV-B19.

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