Parvovirus B19–associated Systemic Lupus Erythematosus: Clinical Mimicry or Autoimmune Induction?

To the Editor:

Recent research has focused on the role of parvovirus B19 in the etiopathogenesis of systemic lupus erythematosus (SLE). The acute manifestations of B19 infection, including symmetric polyarthritis, cytopenia, and macular erythema, bear striking similarity to those found in SLE. Further, infection with B19 elicits autoantibodies to antigens commonly found in patients with SLE, including nuclear antigens, dsDNA, and phospholipids[1]. These symptoms and laboratory abnormalities are transient in some cases, yet persist in others, sparking debate over whether the similarities observed between acute B19 infection and SLE are mere coincidence, or whether the virus does in fact induce chronic autoimmunity. We describe a case of SLE possibly triggered by parvovirus B19, and we conducted a literature search to identify other cases in which B19 infection induced either transient or persistent SLE symptoms. To identify potential prognostic factors for the development of persistent disease, we performed a 2-tailed t test (p value for statistical significance = 0.05) to analyze differences in mean antinuclear antibody (ANA) titers in patients with transient versus persistent symptoms.

A 59-year-old woman was referred for a history of urticarial plaques in the setting of fatigue, facial flushing, and polyarthritis of the hands and elbows. Her joint symptoms first developed 2 years ago; at the time, she was treated for presumed rheumatoid arthritis. However, she subsequently developed urticarial plaques on the torso, back, and arms. Biopsy of a plaque revealed an upper dermal angiocentric mixed polynuclear and mononuclear cell inflammatory infiltrate with leukocytoclasia and occasional eosinophils, consistent with urticarial vasculitis. Complete blood count, serum protein electrophoresis, and hepatitis B and C panels were all normal. However, indirect immunofluorescence for ANA was positive at a titer of 1:1280, speckled pattern. Rheumatoid factor and anticyclic citrullinated peptide were both negative. Treatment with concomitant hydroxychloroquine, prednisone, and hydroxyzine did not relieve her symptoms. As she was not G6PD-deficient, she was started on dapsone 100 mg daily, which temporarily relieved her symptoms. However, 3 weeks later, she was hospitalized for an episode of pancytopenia in the setting of hypotension, malaise, fever, and subjective "brown urine." Four days into hospitalization, testing for parvovirus serologies (Quest Diagnostics, Chantilly, VA, USA) revealed IgM antibody levels of 0.4 (normal < 0.9 index) and IgM + IgG antibody levels of 7.4 (normal < 0.9 index). Although IgM antibody levels were within the normal range at the time, levels continued to wane, to 0.0 one month after hospitalization. Thus, we may have been just outside the window to identify active infection. The patient recovered without sequelae and was restarted on prednisone 10 mg daily. At her initial visit with us, 3 months after hospitalization, she continued to complain of fatigue and frequent, sporadic, urticarial eruptions, although there were no active urticarial lesions on examination. Physical examination was significant for facial macular erythema as well as symmetric swelling of the metacarpophalangeal and proximal interphalangeal joints. Laboratory values at the time were again significant for a positive ANA, 1:2560, speckled pattern, as well as positive anticardiolipin IgM. Anti-Sm, anti-RNP, anti-Scl-70, anti-SSA, and anti-SSB antibodies were negative. Parvovirus B19 IgG was positive at 9.6 (normal < 0.9). On the basis of clinical, serological, and histological findings, we diagnosed an urticarial vasculitis in a patient with SLE, meeting 4 American College of Rheumatology (ACR) criteria. Despite concomitant treatment with prednisone, hydroxychloroquine, and methotrexate, her joint symptoms, malar rash, and frequent urticarial eruptions persist.

In addition to our case, we identified 9 others in the literature in which B19 infection produced transient SLE symptoms[2,3,4,5,6,7,8,9], and 10 cases in which clinical and serological manifestations persisted at least a year following infection[9,10,11,12,13,14,15,16]. In all these cases, B19 IgM serologies were positive at the onset of clinical symptoms. In 7 cases, B19 polymerase chain reaction was also positive. Epidemiological data are summarized in Table 1. Clinical and serological American College of Rheumatology (ACR) criteria are summarized in Tables 1 and 2, respectively.

Aside from autoantibody production, the most common SLE criteria fulfilled were arthritis, cytopenia, and malar rash. As these are all manifestations of acute B19 infection, it is possible that the symptoms observed in the 9 transient cases were manifestations of an acute B19 infection that coincidentally resembled SLE.

Table 1. Epidemiological and clinical data and total number of American College of Rheumatology (ACR) criteria in patients with parvovirus B19 infection and symptoms of SLE. Although it is an ACR criterion, discoid rash was never observed

	Reference	Sex	Age, yrs	No. of ACR Criteria	Arthritis	Malar Rash	Oral Ulcers	Photo-sensitivity	Serositis	Renal	Neurologic
Transient (T)	5	F	37	4	Shoulder, wrist, knee, PIP	—	—	—	—	—	—
	6	F	29	5	Wrist, knee, PIP	+	—	—	—	—	—
	7	F	31	4	Wrist, PIP, MCP	+	—	—	—	—	—
	7	F	28	4	Wrist, knee, PIP	+	—	—	—	—	—
	8	F	44	5	Wrist, PIP, MCP	—	—	—	—	+	—
	9	F	27	5	+ (location NI)	+	—	—	—	—	—
	10	F	39	4	Wrist, PIP, MCP	+	+	—	—	—	—
	11	F	34	4	PIP, MCP	—	—	+	—	—	—
	12	F	36	4	+ (location NI)	—	—	—	—	—	—
Persistent (P)	12	F	38	4	+ (location NI)	+	—	—	—	—	—
	13	F	26	6	Ankle, wrist, knee, PIP	+	—	—	PC	—	—
	14	F	19	5	Ankle, wrist, knee, PIP, MCP	+	—	—	—	—	+
	15	F	46	4	Ankle, shoulder, wrist, knee, PIP, MCP	+	—	—	—	—	—
	16	F	59	6	Shoulder, wrist, PIP, MCP	+	—	—	PL	—	—
	17	F	39	5	PIP	—	—	—	PL, PC	+	—
	18	M	18	5	Ankle, shoulder, wrist, knee, PIP	—	—	—	—	+	—
	18	F	27	5	—	+	+	—	—	—	—
	19	F	82	5	+ (location NI)	—	+	—	PL, PC	—	—
	20	F	72	4	+ (location NI)	—	—	—	—	—	—

PIP: proximal interphalangeal joints; MCP: metacarpophalangeal joints; PL: pleuritis; PC: pericarditis; NI: not indicated.

Table 2. Laboratory data in patients with parvovirus B19 infection and symptoms of SLE.

	Reference	Cytopenia*	ANA Titer*	Anti-dsDNA**	Anticardiolipin**	Other Antibodies	Low Complement
Transient (T)	5	t	1:160	+	NI		+
	6	nha, l, t	1:320	+	Neg		NI
	7	l	1:160	Neg	Neg		NI
	7		1:320	Neg	+	Anti-SSB, Anti-Scl-70	NI
	8	nha, l, t	1:80	+	NI		+
	9	nha, l, t	1:320	Neg	+		NI
	10		1:80	Neg	NI		+
	11		NI	+	NI	Anti-Sm	NI
	12	ha, l	1:160	+	NI	Anti-SSB, Anti-RNP	+
Persistent (P)	12	nha	1:160	+	NI	Anti-SSA	NI
	13	l, t	1:640	+	NI		+
	14		1:1280	+	NI		NI
	15		1:1280	NI	+		NI
	16	nha, l, t	1:2560	+	Neg		NI
	17	nha	1:2048	+	NI		NI
	18	l	1:5120	+	+	Anti-RNP	+
	18	ha, l, t	1:640	+	+	Anti-Sm, Anti-RNP	+
	19	ha, l, t	1:1280	+	+		+
	20	t	1:1000	+	NI		NI

* Denotes American College of Rheumatology (ACR) criterion (with the exception of nonhemolytic anemia). ** Either anti-dsDNA or anticardiolipin fulfill the ACR criteria for "immunologic disorder." ANA: antinuclear antibody; ha: hemolytic anemia; nha: nonhemolytic anemia; l: leukopenia; t: thrombocytopenia; NI: not indicated.

Nevertheless, the 10 cases in which symptoms persisted more than a year lend support to the theory of viral-induced autoimmunity. Other subtleties in the data also support this theory. For example, while the anemia of SLE is hemolytic, the anemia of B19 infection is typically associated with bone marrow suppression. Interestingly, however, our review noted 2 cases of B19 infection associated with an SLE-like hemolytic anemia in patients who did not previously carry diagnoses of SLE — 1 with transient symptoms and 1 with persistent disease. Further, many patients had accompanying ACR criteria that are not known to be associated with acute B19 infection, such as serositis, alopecia, renal involvement, and central nervous system involvement. Perhaps the strongest evidence that B19 may indeed induce SLE rests on similarities in autoantibody production. ANA titers were positive in all patients, while 31.6% had anticardiolipin antibodies. Evidence for viral-induced autoimmunity is particularly strong in the case of autoantibodies highly specific for SLE. Anti-dsDNA, for example, which has a specificity of 75%–100%, occurred in 73.7% of patients in our review.

The degree of autoantibody production may also predict which patients develop persistent disease. While ANA titers were positive (> 1:40) for all patients, the 9 patients with a self-limited SLE course had ANA titers of 1:320 or less, while 9/10 patients who developed persistent SLE had titers of at least 1:640 at the time of diagnosis. After normalizing values to an equivalent deviation by taking the logarithm of the exponential ANA data, there was a statistically significant difference in the mean ANA titers for those with transient SLE compared to those with persistent SLE ($p = 0.000142$; estimated difference in means –2.7; 95% CI –3.86 to –1.55).

While the clinical and laboratory manifestations of B19 infection and SLE overlap, establishing a direct causal role remains difficult due to the brief window of opportunity during which to establish the diagnosis with IgM antibody serology. This was indeed the case for our patient: although IgM antiparvovirus B19 antibody levels were within the normal range during hospitalization, their steady decline — dropping 33% in just 1 week — may suggest true prior infection. We hypothesize that our patient may have had a subclinical B19 infection prior to initiating dapsone; the combination of acute B19 infection and dapsone administration then synergistically led to aplastic crisis.

There is mounting evidence that B19 may be a precipitating factor for the development of SLE. Based on our review, arthritis, malar rash, cytopenias, and elevated ANA, anti-dsDNA, and anticardiolipin titers are among the most common manifestations of parvovirus B19–associated SLE. Further, based on our data, the relative ANA titer at the onset of infection may be a good prognostic indicator as to which patients develop chronic B19–induced SLE as opposed to mere transient symptoms.

MEGHAN T. HESSION, BS; SHIU-CHUNG AU, MD, Department of Dermatology, Tufts Medical Center, 800 Washington Street, Boston, Massachusetts 02111, USA; ALICE B. GOTTLIEB, MD, PhD, Tufts Medical Center and Tufts University School of Medicine. Address correspondence to M.T. Hession; E-mail: mth2114@columbia.edu

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