

## A pediatric case with parvovirus B19-associated uveitis without autoantibody formation

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### ABSTRACT

Acute parvovirus B19 (B19) infection is often accompanied by autoantibody formation, including antinuclear antibodies and rheumatoid factor, and the symptoms of the infection are similar to those of several autoimmune diseases. Uveitis is a representative manifestation of autoimmune diseases and is rarely caused by B19. Autoantibody formation was confirmed in 2 previously reported cases with B19-associated uveitis. However, whether B19-associated uveitis is caused by the direct invasion of the virus or the induction of autoimmunity remains unclear. We herein report a pediatric case with B19-associated uveitis without autoantibody formation. We speculated that B19 might have directly invaded the eye in this patient because of the development of uveitis without antibody formation and the negative results for anti-B19-specific antibodies in the serum at the onset of the disease. Although the mechanism of invasion is unknown, B19 may have a high affinity for tissue in the eye.

**Keywords:** uveitis, parvovirus B19, autoantibodies, direct invasion

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### INTRODUCTION

Parvovirus B19 (B19) is commonly known as a causative pathogen of erythema infectiosum in children. The virus also provokes various severe diseases, such as hematological disorders, hepatitis and encephalitis.<sup>1-3</sup> Acute B19 infection is often accompanied by autoantibody formation, including antinuclear antibodies (ANA) and rheumatoid factor (RF), and the symptoms of the infection are similar to those of several autoimmune diseases.<sup>4</sup> Uveitis is a representative manifestation of autoimmune diseases and is sometimes caused by various pathogens. Three cases with B19-associated uveitis were previously reported,<sup>5-7</sup> but the pathophysiology was unknown. We herein report the first pediatric case of B19-associated uveitis without autoantibody formation during the acute phase of primary infection of B19.

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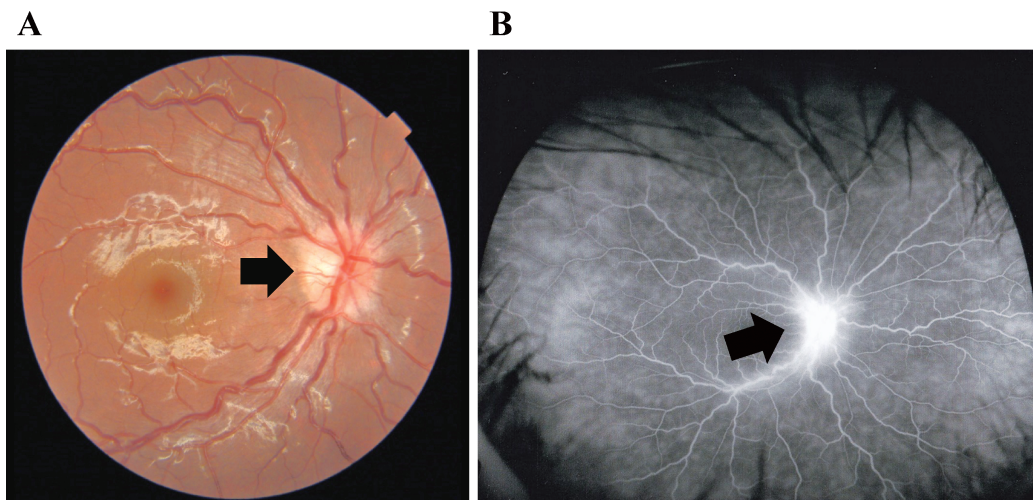
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## CASE REPORT

A previously healthy 9-year-old boy visited our hospital for the evaluation and treatment of uveitis. Seven days before the initial visit, bilateral redness of the bulbar conjunctiva was noted, and the patients developed a fever and ophthalmalgia 5 days before the initial visit. An ophthalmic medical practitioner diagnosed him with iritis. He was referred to us for further management. He was already afebrile at the initial visit to our hospital. No abnormal physical findings were revealed, except for redness of the conjunctiva. The presence of a large amount of cells in the anterior chamber (3+) and bilateral papilledema on direct ophthalmoscopy and dye leakage from retinal vessels in fluorescein fundus angiography led to the diagnosis of panuveitis (Fig. 1).

Complete blood counts showed a leukocyte count of  $8.9 \times 10^9$  /L with 82% neutrophils, a hemoglobin concentration of 13.6 g/dL and a platelet count of  $299 \times 10^9$  /L. Blood chemistry analyses showed an aspartate aminotransferase level of 91 IU/L, an alanine aminotransferase level of 155 IU/L and a lactate dehydrogenase level of 279 IU/L. The C-reactive protein concentration was 2.27 mg/dL, and the erythrocyte sedimentation rate was 59 mm/h. Neither hypocomplementemia nor hypergammaglobulinemia was shown. ANA, anti-double stranded DNA antibodies and anti-SSA and anti-SSB antibodies were undetectable, and RF (4.3 U/mL, reference range < 15) and angiotensin-converting enzyme (6.8 IU/L, reference range 8.3–21.4) were not elevated. Serologic tests for *Toxoplasma gondii*, *Bartonella henselae* and human T-cell leukemia virus type 1 indicated no previous infection, and that for cytomegalovirus showed a past or current inactive infection. The ophthalmalgia and redness of the conjunctiva were ameliorated after starting topical steroid therapy, whereas mild papilledema persisted. Three weeks after the onset of symptoms, erythema of the bilateral cheeks and upper arms appeared. Serum anti-B19 IgM antibody was positive. Neither ANA nor RF was elevated. B19-DNA was detected from the serum sample obtained at the initial visit to our hospital ( $1 \times 10^7$  copies/mL), whereas anti-B19 IgG and IgM antibodies were undetectable. Based on these results, we diagnosed him with B19-associated uveitis. The abnormal fundusoscopic findings disappeared at the 5th month of illness with continuous topical steroid therapy alone.



**Fig. 1** Fundusoscopic findings at the initial visit to our hospital. Papilledema (black arrow) was found on direct ophthalmoscopy (A) and fluorescein fundus angiography showed dye leakage (black arrow) from retinal vessels (B).

## DISCUSSION

Only 1 of the 3 previously reported cases developed B19-associated uveitis before the appearance of erythema (Table 1),<sup>5-7)</sup> indicating that the present case was the second reported case with the disease during the acute phase of B19 infection. Whether B19-associated uveitis is caused by the direct invasion of the virus or the induction of autoimmunity remains unclear. Autoantibodies, which are believed to play a central role in the development of autoimmune disorder-related uveitis,<sup>8)</sup> are often detected during B19 infection. In a previous study, ANAs were detected in 65% of patients with B19 infection.<sup>9)</sup> Two reported cases of B19-associated uveitis showed elevated levels of autoantibodies and positive results (Table 1), thus indicating that autoantibodies appear to play some role in the immunological process.<sup>6-7)</sup> However, the prevalence of antibodies against non-structural protein NS-1 of B19 and the detection rate of viral DNA in the serum were higher in the patients with uveitis than in healthy individuals.<sup>10)</sup> Serum anti-B19-specific antibodies in the present case were undetectable at the onset of uveitis, and no autoantibody formation occurred over the course of the disease, suggesting that B19 might directly invade the eye.

There is no specific treatment for the elimination of B19. Intravenous immunoglobulin (IVIG) therapy is performed for immunocompromised patients with chronic B19 infection, patients with chronic hemolytic disorders or patients with severe B19 infection, including encephalitis and myocarditis,<sup>11-14)</sup> whereas B19 infection spontaneously improves in immunocompetent patients. In the present case, uveitis was not worsened at the diagnosis of erythema infectiosum. As erythema usually appears after the viremia has cleared, IVIG therapy was not needed for the present patient. However, topical steroid therapy seemed to be necessary in the present case because of the limited therapeutic options available for childhood uveitis of unknown etiology.<sup>15)</sup>

B19 is preferentially replicated in erythroid progenitor cells but has also been found to persist in many other non-erythroid tissues.<sup>16)</sup> B19 capsid RNA or proteins have been detected in tissues from the colon, heart, liver and lymphoid, synovial, testicular and thyroid and have been associated with increased inflammatory-related gene expression.<sup>16,17)</sup> However, the mechanism underlying the invasion to these tissues is unknown. The present case suggests that B19 may also have a high affinity for tissue in the eye. The accumulation of more patients with B19-associated uveitis is needed to determine the pathophysiology of the development of the disease.

**Table 1** Reported patients with parvovirus B19-associated uveitis

Pt.	Age	Sex	Appearance of erythema	Timing of the onset of uveitis	Autoantibody detected from sera	Treatment	Outcome	Complication	Ref.
1	18	F	Yes	After a few weeks of the appearance of erythema	Unknown	Topical steroid	Improved	Adie's pupils	5
2	6	F	No	Development of only uveitis	RF	Topical steroid	Improved		6
3	5	F	Yes	Before 2 weeks of the appearance of erythema	ANA	Topical steroid	Improved	Epilepsy	7
4	9	M	Yes	Before 3 weeks of the appearance of erythema	None	Topical steroid	Improved		Ours

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## CONFLICT OF INTEREST

None of the authors has conflict of interest with this submission. No financial support was received for this submission.

## REFERENCES

- 1) Kerr JR. A review of blood diseases and cytopenias associated with human parvovirus B19 infection. *Rev Med Virol*, 2015; 25: 224–240.
- 2) Yoto Y, Kudoh T, Haseyama K, Suzuki N, Chiba S. Human parvovirus B19 infection associated with acute hepatitis. *Lancet*, 1996; 347: 868–869.
- 3) Yoto Y, Kudoh T, Haseyama K, Tsutsumi H. Human parvovirus B19 and meningoencephalitis. *Lancet*, 2001; 358: 2168.
- 4) Page C, François C, Goëb V, Duverlie G. Human parvovirus B19 and autoimmune diseases. Review of the literature and pathophysiological hypotheses. *J Clin Virol*, 2015; 72: 69–74.
- 5) Corridan PG, Laws DE, Morrell AJ, Murray PI. Tonic pupils and human parvovirus (B19) infection. *J Clin Neuroophthalmol*, 1991; 11: 109–110.
- 6) Maini R, Edelsten C. Uveitis associated with parvovirus infection. *Br J Ophthalmol*, 1999; 83: 1403–1404.
- 7) Hsu D, Sandborg C, Hahn JS. Frontal lobe seizures and uveitis associated with acute human parvovirus B19 infection. *J Child Neurol*, 2004; 19: 304–306.
- 8) Caspi RR. A look at autoimmunity and inflammation in the eye. *J Clin Invest*, 2010; 120: 3073–3083.
- 9) Saeki T, Shibuya M, Sawada H, Miyamura S, Nakano M, Gejyo F, *et al.* Human parvovirus B19 infection mimicking systemic lupus erythematosus. *Mod Rheumatol*, 2001; 11: 308–313.
- 10) Heinz C, Plentz A, Bauer D, Heiligenhaus A, Modrow S. Prevalence of parvovirus B19-specific antibodies and of viral DNA in patients with endogenous uveitis. *Graefes Arch Clin Exp Ophthalmol*, 2005; 243: 999–1004.
- 11) Seyama K, Kobayashi R, Hasle H, Apter AJ, Rutledge JC, Rosen D, *et al.* Parvovirus B19-induced anemia as the presenting manifestation of X-linked hyper-IgM syndrome. *J Infect Dis*, 1998; 178: 318–24.
- 12) Crabol Y, Terrier B, Rozenberg F, Pestre V, Legendre C, Hermine O, *et al.* Intravenous immunoglobulin therapy for pure red cell aplasia related to human parvovirus b19 infection: a retrospective study of 10 patients and review of the literature. *Clin Infect Dis*, 2013; 56: 968–977.
- 13) Barah F, Whiteside S, Batista S, Morris J. Neurological aspects of human parvovirus B19 infection: a systematic review. *Rev Med Virol*, 2014; 24: 154–168.
- 14) Stouffer GA, Sheahan RG, Lenihan DJ, Patel P, Lenihan DJ. The current status of immune modulating therapy for myocarditis: a case of acute parvovirus myocarditis treated with intravenous immunoglobulin. *Am J Med Sci*, 2003; 326: 369–374.
- 15) Engelhard SB, Bajwa A, Reddy AK. Causes of uveitis in children without juvenile idiopathic arthritis. *Clin Ophthalmol*, 2015; 9: 1121–1128.
- 16) Adamson-Small LA, Ignatovich IV, Laemmerhirt MG, Hobbs JA. Persistent parvovirus B19 infection in non-erythroid tissues: possible role in the inflammatory and disease process. *Virus Res*, 2014; 190: 8–16.
- 17) Polcz ME, Adamson LA, Lu X, Chang MN, Fowler LJ, Hobbs JA. Increased IL-6 detection in adult and pediatric lymphoid tissue harboring parvovirus B19. *J Clin Virol*, 2013; 57: 233–238.