Symptomatic parvovirus B19 infection caused by blood component transfusion

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BACKGROUND: Although a risk of transfusion-transmitted human parvovirus B19V (TT-B19V) infection has been a concern, there have been very few reports of clinically relevant TT-B19V caused by the transfusion of a B19V-containing blood component. It has therefore been a matter of debate whether a universal B19V screening with an appropriate sensitivity is required.

STUDY DESIGN AND METHODS: Through the Japanese Red Cross hemovigilance system, clinical reports on possible TT-B19V were collected from 1999 to 2008, during which B19V donor screening (sensitivity, 10^{10} IU/mL) was conducted and repository blood samples from donors were available.

RESULTS: Eight patients with TT-B19V caused by component transfusion have been identified. Four patients developed sustained anemia and pure red blood cell (RBC) aplasia and one patient developed pancytopenia. The underlying diseases in these five patients were either hematologic malignancy or hemolytic diseases. The viral loads of the responsible components for these cases ranged from 10^3 to 10^8 IU/mL. Two patients who underwent surgical treatment without any hematologic disorder exhibited only moderate symptoms. The B19V DNA sequence identity between a patient and the linked blood donor was confirmed in five of the eight patients. All of the components responsible for the eight cases were positive for anti-B19V immunoglobulin (Ig)M.

CONCLUSION: Vulnerability to serious B19V-related hematologic disorders depended on the patient's underlying disease state of an enhanced erythropoiesis, not on the viral load of the component transfused. To prevent clinically relevant TT-B19V, a strategy is suggested in which patients at risk of acquiring RBC aplasia or pancytopenia are targeted.

Infection by human parvovirus B19 (B19V) is common in any geographic area and causes erythema infectiosum or fifth disease in childhood. The infection in adults is usually asymptomatic but may cause a transient red blood cell (RBC) aplasia in patients in the state of an enhanced erythropoiesis or may cause persistent anemia in immunocompromised patients.[1-3] The prevalence of anti-B19V immunoglobulin (Ig)G increases steadily even after childhood, suggesting that B19V infection occurs frequently during adulthood.[3-6] In acute infection, the viral load in peripheral blood reaches as high as 10^{12} IU/mL.[7] The frequent primary infection among adults and the high viral load without symptoms imply the presence of a considerable number of blood donors with a high viral load, which raises the possibility of a considerable risk of transfusion-transmitted B19V infection (TT-B19V).

Although TT-B19V cases have often been reported after the transfusion of plasma derivatives,[8-10] there have been very few reports of clinically relevant B19V infection that is considered as a result of the transfusion of a B19V-containing blood component (i.e., RBCs, fresh-frozen plasma [FFP], or platelet [PLT] concentrates).[11-15] It has

ABBREVIATIONS: AML = acute myeloid leukemia; B19V = human parvovirus B19; JRC = Japanese Red Cross; nt = nucleotide(s); RHA = receptor-mediated hemagglutination; TT-B19V = transfusion-transmitted human parvovirus B19V; TTI(s) = transfusion-transmitted infection(s).

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therefore been a matter of debate whether a universal B19V screening with an appropriate sensitivity is indeed required for securing blood component safety. In this regard, several studies have been conducted to establish the frequency of blood products harboring TT-B19V risk and the frequency of clinically relevant TT-B19V cases. In most such studies, a reason to implement a B19V screening method that covers all blood donations has not been verified because no case of clinically relevant TT-B19V was identified during the study period.[16-18]

Japanese Red Cross (JRC) blood centers established a hemovigilance system in 1993 and have been collecting voluntary reports on transfusion-transmitted infections (TTIs) and other adverse effects as a result of transfusion. Through the system, JRC has so far obtained five established and three probable cases of TT-B19V. In this article, we describe the details of TT-B19V cases, each of which represented a typical clinical course of B19V infection.

PATIENTS AND METHODS

Hemovigilance system

JRC blood centers are the sole facilities in Japan that deal with blood procurement and processing, testing, and delivery of blood components. The JRC hemovigilance system has been functioning since 1993 and covers the entire country with 1 million patients being transfused every year. Although the reporting of suspected TTI cases to JRC is not mandatory, it is obligatory for every physician to report TTI cases to the Japanese Ministry of Health, Labour and Welfare, which in turn refers this information to JRC. Eventually, JRC is able to obtain all information on suspected TTIs and other serious adverse reactions caused by blood transfusion. The system also includes a complete sample archive from all blood donations since 1999, which enables us to investigate the cause of a TTI using the repository blood samples obtained from the donation associated with the TTI. For TT-B19V cases, a lookback study for the possibility of previous donation with viremia has not been performed.

Receptor-mediated hemagglutination assay

In 1998, JRC implemented a receptor-mediated hemagglutination (RHA) assay as a screening test for B19V and used it for all donated blood until 2007. The theoretical basis of the RHA assay system was described elsewhere[19,20]; briefly, it is a B19V antigen detection method in which the indicator RBCs agglutinate via B19V particle binding to globosides on the RBC membrane at a critical pH (pH 5.6 $\pm$ 0.1). The sensitivity of RHA is approximately 10^{10} IU/mL, and by this method, 300 to 400 B19V-positive donors with very high titer viremia have been identified every year.[21] Although the sensitivity of RHA is not satisfactory, it has greatly contributed to the lowering of the viral load in a plasma pool that is manufactured into plasma derivatives.[22] In 2008, JRC implemented a chemiluminescence enzyme immunoassay–based screening assay that is also an antigen detection assay with a sensitivity of approximately 10^7 IU/mL.

Polymerase chain reaction analysis of B19V and antibody detection

On receiving a report of a suspected case of TT-B19V, polymerase chain reaction (PCR) analysis was carried out to detect the B19V DNA in patient sera obtained before and after the index blood transfusion as well as in repository tube(s) obtained from the donation(s) from which the blood component(s) suspected of causing TT-B19V had been processed. B19V DNA was extracted using a total nucleic acid isolation kit (MagNA Pure LC, Roche Diagnostics, Tokyo, Japan) and amplified and quantified using a B19V quantification kit (LightCycler, Roche Diagnostics, Tokyo, Japan). The forward and reverse primers were located at Nucleotides (nt) 2046 to 2064 and nt 2110 to 2092, respectively. The probe used was mapped at 24 bp of nt 2067 to 2090. The 95% detection limit of the PCR system is 289 IU/mL, as determined by probit analysis. Direct B19V DNA sequencing was performed targeting 1069 bp (nt 1884-2952) in the NS1/VP1 region for Cases 1 to 4.[23] As for Case 5, B19V DNA was sequenced for a total of 1913 bp covering the NS (489 bp [nt 1396-1884] and 225 bp [nt 1962-2187]), NS-VP1 (597 bp [nt 2370-2966]), and VP1 (602 bp [nt 2984-3585]) regions. Sequence identity was assessed for these regions between the patient sample and the blood donor sample. IgM and IgG specific for B19V were detected by enzyme-linked immunosorbent assay (Parvo-IgM and Parvo-IgG, Denka Seiken, Tokyo, Japan).

RESULTS

The annual number of blood donations in Japan is approximately 5 million and the annual number of components released to medical facilities for RBCs, FFP, and PLT concentrate are 3.3 million, 960,000, and 730,000, respectively. Data presented in this article were collected during the period from 1999 through 2008 when repository blood samples from donors were available. During that period, JRC received only 15 reports of suspected TT-B19V from physicians, among which we were able to identify eight cases of TT-B19V. This indicates that the case frequency of documented TT-B19V is eight per 50 million or approximately one in 6 million donations. Details of the five TT-B19V cases that were confirmed by B19V-DNA sequence analysis are described below (Table 1).

Case 1

A 41-year-old man with hairy cell leukemia underwent a treatment regimen including a course of cladribine

TABLE 1. Cases established as having TT-B19V infection

Case	Patient profile	Before transfusion	After transfusion	Symptoms and laboratory findings	Transfused components
1	41, male Hairy cell leukemia After chemotherapy		DNA (+) IgM (+) IgG (+)	RBC aplasia (3 months) Reticulocytopenia (1 month) Viremia level of 1×10^{12} copies/mL	RBCs (irradiated) DNA (+) 1.8×10^5 IU/mL* 2×10^6 IU/bag† IgM (+) IgG (+)
2	57, male AML (M4) After chemotherapy	DNA (–) IgM (–) IgG (–)	DNA (+) IgM (+) IgG (+)	Pure RBC aplasia (approx. 2 months)	PC (irradiated) DNA (+) 9.7×10^8 IU/mL 2×10^{10} IU/bag IgM (+) IgG (–)
3	35, female Placenta previa	DNA (–) IgM (–) IgG (–)	DNA (+) IgM (+) IgG (+)	Fever Systemic eruption (3 weeks)	RBCs (irradiated) DNA(+) 3.0×10^5 IU/mL 3×10^6 IU/bag IgM (+) IgG (+)
4	59, male Rectal cancer	DNA (–) IgM (–) IgG (–)	DNA (+) IgM (+) IgG (+)	Sustained high fever (5 days)	RBCs (irradiated) DNA(+) 5.1×10^3 IU/mL 5×10^4 IU/bag IgM (+) IgG (+)
5	61, male AML After chemotherapy	DNA (–)	DNA (+)	High fever Disseminated erythema Pure RBC aplasia (7 weeks) Reticulocytopenia	PC (irradiated) DNA (+) IgM (+) IgG (+)

* Viral concentration in the donated blood.
† Estimated viral load in the component.
PC = PLT concentrate.

(2-chlorodeoxyadenosine) for 7 days in May 2005. On Day 0, 9 days after the completion of cladribine treatment, he was transfused with 1 unit of RBCs because of anemia. The reticulocyte proportion in his peripheral blood decreased from 3.6% on Day 6 to 2.4 and 0.3% on Days 8 and 10, respectively. B19V PCR analysis was performed on his Day 11 serum, which revealed a viremia level of 1×10^{12} copies/mL. The JRC central laboratory also detected B19V DNA and anti-B19V of both IgM and IgG classes in sera obtained on Day 22. On the basis of these findings, the diagnosis of RBC aplasia due to TT-B19V was made. Reticulocyte counts ranged from 0.1% to 0.2% since then, and the patient remained RBC transfusion dependent requiring occasional granulocyte–colony-stimulating factor (G-CSF) administration. His reticulocyte count started to increase in late June and the complete resolution of anemia was confirmed in late August. The repository sample from the index donation for the RBCs was found to contain 1.8×10^5 IU/mL B19V DNA as well as anti-B19V of both IgM and IgG classes. The patient was administered G-CSF because of existing leukopenia caused by the preceding chemotherapy with cladribine, not by B19V infection (Y. Tsukada, manuscript in preparation).

Case 2

A 57-year-old man received chemotherapy for acute myeloid leukemia (AML, M4). After the completion of chemotherapy in May 2005, he received multiple blood transfusions because of sustained marrow suppression. The index blood transfusion of the PLT concentrate responsible for TT-B19V was carried out on June 14 (Day 0). A delayed recovery of RBC generation was noted despite a complete recovery of white blood cell and PLT generation. Marrow examination was carried out on Day 21 revealing pure RBC aplasia as well as a complete remission of AML. His peripheral blood sample collected on Day 24 was positive for B19V DNA and anti-B19V of both IgM and IgG classes. He became negative for anti-B19V IgM on Day 35 and RBC generation recovery was recognized 1 month later. A pretransfusion sample obtained on Day –21 was negative for both B19V DNA and anti-B19V of both classes. The repository sample from the index donation for the PLT concentrate contained 9.7×10^8 IU/mL B19V DNA and the anti-B19V of the IgM class but not that of the IgG class. Seventeen blood components had been transfused to this patient before the marrow examination, but only the repository sample from the index PLT concentrate was positive for B19V DNA.

Case 3

A 35-year-old woman with placenta previa received a transfusion of 5 units of RBCs in June 2005 because of massive bleeding on delivery. On Day 7 after the index transfusion, she developed a fever of 38°C. Four days later she developed systemic small eruptions, which led her physician to suspect a viral infection. Laboratory testing revealed the presence of anti-B19V IgM in the blood sample collected on Day 12. All the symptoms disappeared 1 month after transfusion without specific medication. The pretransfusion sample collected on Day 0 was found to be negative both for B19V DNA and anti-B19V of both IgM and IgG classes. Posttransfusion samples obtained on both Day 47 and Day 60 contained B19V DNA and anti-B19V of both classes. A retrospective study revealed that a repository sample from 1 of the 5 units of the RBCs contained 3.0×10^5 IU/mL B19V DNA as well as anti-B19V of both classes.

Case 4

A 59-year-old man with rectal cancer received a transfusion of 2 units of RBCs during a surgical operation in April 2006. Although his postoperative course was uneventful for 5 days, he developed a high fever of 38 to 40°C on Day 6 postoperation and the fever remained for 5 days despite medication with antibiotics and antipyretics. The fever thereafter resolved spontaneously. It was reported that a surgical complication was unlikely from the viewpoints of the operative procedure and postoperative course. A posttransfusion sample collected on Day 22 was found to be positive for B19V DNA and anti-B19V of both IgM and IgG classes: these three markers were all negative in a pretransfusion sample obtained 1 day before operation. A repository sample from the donation for 1 of the 2 units of the RBCs transfused contained 5.1×10^3 IU/mL B19V DNA as well as anti-B19V of both IgM and IgG classes.

Case 5

A 61-year-old man undergoing chemotherapy for AML received 24 blood transfusions for 4 months in 2002. He developed a high fever and disseminated erythema 22 and 26 days after the index transfusion (Day 0), respectively. Reticulocytopenia developed and pure RBC aplasia was confirmed by marrow examination. B19V DNA was not detected in his pretransfusion sample collected on Day –49 but was detected in his posttransfusion sample collected on Day 25. He recovered from pure RBC aplasia 7 weeks after the transfusion. The responsible blood component was a PLT concentrate transfused in mid-May, which was found to be positive for anti-B19V of both IgM and IgG classes and B19V DNA. Data on the B19V DNA concentration in the repository sample from the index component are not available.

In the first four cases presented above, complete genome sequence identity was established for nt 1884 to 2952 of B19V between the patient posttransfusion samples and the associated donor repository samples. For Case 5, viral sequence identity was established for a total of 1913 bp (see Patients and Methods). Figure 1 presents a phylogenetic tree of the B19V DNA sequences for the five established cases.

In addition to these five cases with established B19V DNA sequence identity between donors and recipients, JRC blood centers have three reports of probable cases of TT-B19V (Table 2). In all three cases, B19V DNA was detected in posttransfusion samples and linked donor repository samples, but data on B19V DNA sequence analysis were not available. The first case was reported elsewhere in detail[15]; briefly, a 52-year-old woman with paroxysmal nocturnal hematuria was regularly receiving RBC transfusions with prednisolone administration. She developed pancytopenia with high fever and general malaise 13 days after the index transfusion (Day 0). She thereafter received a continuous course of transfusions with RBCs and PLT concentrates together with G-CSF. She recovered from pancytopenia approximately 1 month after the index transfusion, although the reticulocyte proportion remained low for a longer period. Anti-B19V IgM was detected in her posttransfusion samples with increasing titer in the following months. Before the onset of pancytopenia, the patient had received transfusion of 1 unit of RBCs on Days –56, –32, 0, and +1. Repository blood samples from the four components were subjected to PCR analysis and only one sample from the index blood component was verified to be positive for B19V DNA. Strikingly, the B19V DNA–positive blood component attributed to this infection was a washed RBC unit processed from a donation containing 6.8×10^3 IU/mL B19V and anti-B19V of both IgM and IgG classes. The blood obtained 4 months later from the same donor still had a viral load of 1.6×10^3 IU/mL but no specific IgM. The second patient was a 28-year-old woman with hemolytic anemia. She sustained a prolonged severe anemia after transfusion of 1 unit of RBCs. Marrow examination verified hypoplasia of a RBC lineage. The proportion of peripheral blood reticulocytes remained as low as 0.1% for 1 month. B19V DNA was not detected in her pretransfusion sample. The blood component responsible for this case was an RBC unit positive for anti-B19V of both IgM and IgG classes. The third patient was a 79-year-old man who received transfusion of 1 unit of RBC during pelvic tumor resection. He did not develop any clinical symptoms after the transfusion but routine postoperative blood analysis revealed a decreased reticulocyte count that lasted for 1 week. Further investigation verified the anti-B19V IgM conversion. The responsible RBC unit contained anti-B19V of both IgM and IgG classes.

In one of the three probable cases presented above, B19V DNA was negative in the pretransfusion sample,

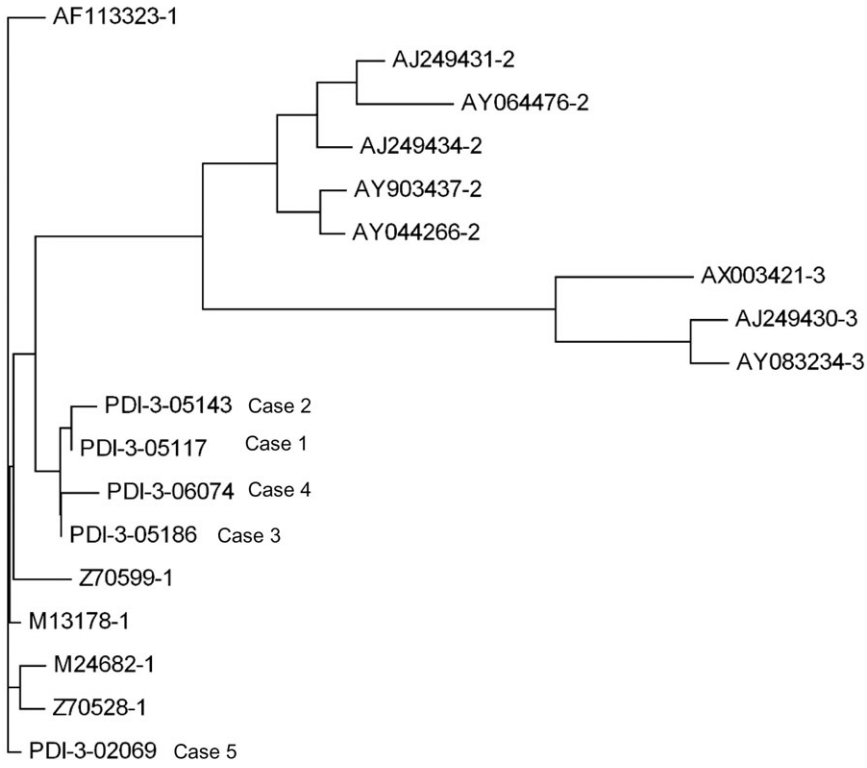

Fig. 1. Phylogenetic tree of B19V DNA for five established cases. PDI-3-05117, -05143, -05186, -06074, and -02069 correspond to Cases 1, 2, 3, 4, and 5, respectively. For these cases, the B19V DNA sequence was identical between those obtained from blood donors and those from transfused patients for the region indicated under Patients and Methods. As references, other sequences published in GenBank from Genotypes 1 to 3 are also shown.

TABLE 2. Probable cases of TT-B19V infection

Case	Patient profile	Before transfusion	After transfusion	Symptoms and laboratory findings	Transfused components
1	52, female Paroxysmal nocturnal hematuria		DNA (+) IgM (+)	High fever General malaise Pancytopenia (1 month)	Washed RBCs (irradiated) DNA (+) 6.8×10^3 IU/mL* IgM (+) IgG (+)
2	28, female Hemolytic anemia	DNA (–)	DNA (+)	Prolonged severe anemia RBC hypoplasia Reticulocytopenia (1 month)	RBCs (irradiated) DNA (+) IgM (+) IgG (+)
3	79, male Pelvic tumor		DNA (+) IgM (+)	No symptoms Reticulocytopenia (1 week)	RBCs (irradiated) DNA(+) IgM (+) IgG (+)

* The washed RBCs were processed from blood containing 6.8×10^3 IU/mL B19V DNA.

whereas in the other two cases, anti-B19V IgM was positive in the posttransfusion samples, which supports the notion that these three are TT-B19V cases as well.

DISCUSSION

We described in this report five established and three probable TT-B19V cases, seven of which showed overt clinical illness. The association of the B19V infection with transfusion was proved by serologic data available and viral sequence homology analysis. From a phylogenetic tree of B19V DNA for the five established cases (Fig. 1), it is apparent that the five pairs of B19V DNA all belonging to Genotype 1 are very close but distinct genomes.

There have been only five previously reported cases of TT-B19V caused by the transfusion of blood

components,[11-15] one of which was cited in this article as a probable case.[15] Although the TRIP Dutch National Hemovigilance reported one possible case of TT-B19V in 2007,[24] there has been no report of TT-B19V in the literature published by hemovigilance systems in other countries including SHOT in the United Kingdom and hemovigilance in France. One asymptomatic case of TT-B19V has recently been reported during a donor-linked prospective study.[18] The possible reasons for the paucity of the reports are as follows: 1) a considerable proportion of transfusion recipients are immune to B19V. 2) B19V infection usually does not cause a serious illness even in nonimmune adults but results in a deleterious outcome only in a small proportion of patients who are in the specific conditions described above. 3) Passive immunization by the transfer of neutralizing anti-B19V often occurs with concurrent transfusion.[6] 4) The risk factors that increase susceptibility of recipients to severe B19V disease, and the signs and symptoms of TT-B19V infection, are not well recognized among physicians.

In view of almost the same B19V seroprevalence in Japan and western countries,[2,13,25] it is inconceivable that we encountered these cases because B19V infection is more common in Japan. It is also unlikely that the B19V genotype commonly found in Japan is more virulent and causes more serious illnesses in transfusion recipients because the B19V genome variance is small in a defined genotype and the B19V genotypes found in the established cases are all Genotype 1, the type commonly found in western countries. Moreover, B19V-related serious illnesses as a result of infusion of B19V-contaminated plasma derivatives have often been reported in western countries.[2] We speculate that we were able to collect TT-B19V cases owing to the efficient hemovigilance system of JRC. It should also be noted that physicians are very cooperative in reporting suspected TTIs to blood centers, which is possibly facilitated because JRC laboratories are capable of investigating the causality of TTIs using complete sample archives from all blood donations.

If the implementation of a universal B19V screening is under consideration or required by a national authority regulating blood program, it is necessary to establish a cutoff level for screening. In this regard, the infectious dose of B19V DNA in blood components that might cause TTIs has been a subject of debate.[17,26-28] In general, a viral load of approximately 10^5 IU/mL is becoming to be accepted as an infectious dose for TT-B19V. In our clinical observation, the viral concentrations of the components that caused RBC aplasia in susceptible patients were 1.8×10^5 IU/mL in Case 1 and 9.7×10^8 IU/mL in Case 2. The viral concentrations of the components that caused less severe symptoms such as febrile reaction or skin eruption were 3.0×10^5 IU/mL in Case 3 and 5.1×10^3 IU/mL in Case 4. Another patient with probable TT-B19V in our case series developed a sustained pancytopenia after the transfusion of a washed RBC unit processed from a donation containing 6.8×10^3 IU/mL B19V. Although these data may indicate that the components with very low viral loads are infectious, it is yet to be determined whether the lower limit of infectivity is 10^3 or 10^5 IU/mL, because most previous studies have not dealt with the blood components with viral loads in this range and few data are available to determine the lower limit.

While data necessary to determine the infectious dose of B19V in the blood components are still lacking, clinical symptoms due to B19V infection acquired by blood component transfusion appear to be related to the clinical state of the transfusion recipient. Each clinical course of the five established cases described in this report represents typical characteristics of acute B19V infection after a respiratory tract infection that have been described in the literature.[1,3] When a patient with an enhanced erythropoiesis receives a transfusion with a B19V-containing component, the cell production of a lineage susceptible to B19V, mainly the RBC lineage,[29,30] is totally impaired by B19V, which directly leads to RBC aplasia in the marrow and anemia in the peripheral blood because the RBC count or hemoglobin level in their peripheral blood was maintained by the enhanced erythropoiesis as presented in Cases 1, 2, and 5. If a patient has been in the state of immunosuppression, it will delay the elimination of B19V and the recovery of the affected cell lineage in the marrow. The underlying diseases for the two of the three probable cases (i.e., paroxysmal nocturnal hematuria and hemolytic anemia) also represent the typical conditions that could lead to serious hematologic disorders after B19V infection. On the other hand, in recipients who are immunologically competent and not in the state of an enhanced erythropoiesis, B19V transmission may not occur or if TT-B19V occurs it may result in outcomes limited to laboratory findings (e.g., seroconversion or DNA conversion) or moderate symptoms not more severe than a sustained fever, generalized skin lesions, or arthropathy, as shown in Cases 3 and 4. These symptoms subsequently resolved without medication possibly owing to a rapid viral neutralization by their intact immune response before anemia developed. It is possible that the patient in Case 4 presented only mild symptoms not because the viral load of the component was low but because he was not in the state of an enhanced erythropoiesis when transfused. It is, thus, more explainable to consider that the clinical state of the patient rather than the viral load of the component determines the clinical course of TT-B19V. In Cases 2 and 5, there is a slight possibility that the clinical course of acute B19V infection was modified by the passive transfer of neutralizing antibodies from other PLT concentrates transfused. None of the patients presented above received FFP transfusion.

It could, however, be argued that we have identified TT-B19V cases associated with a relatively low viral load

and specific IgM because these cases were identified under the screening by RHA, which detects and excludes very high titer viremic donations. It is therefore possible that TT-B19V associated with low-viral-load component transfusion is only a portion of all TT-B19V cases that could be represented by cases transfused with high-viral-load components.

It is of note that all the components for the three probable TT-B19V cases as well as the five established cases were positive for anti-B19V IgM. In the four cases of TT-B19V reported in the literature except for one probable case described in this article, 2 of the 3 units of transfused components tested were also specific IgM positive.[11,12,14] These findings strongly suggest that the presence of specific IgM in the component with or without specific IgG is a risk factor for TT-B19V. The positivity for specific IgM implies that the donors were in the early recovery phase from an acute primary infection. It is therefore conceivable that the seven blood donors in this study who were also positive for specific IgG had anti-B19V IgG of insufficient titer or an immature specificity that is incapable of full neutralization of B19V, although it has been considered that infectivity is absent or at least modulated once specific IgG is present.

Deep insight is needed to determine whether universal preventive measures should be implemented to eradicate TT-B19V. First, the degree of seriousness of B19V-related illnesses has to be taken into consideration. Sustained fever is uncomfortable and skin lesions are painful to patients but they are essentially benign and self-limited with bearable duration. Although the condition of TT-B19V–related pure RBC aplasia sometimes requires RBC transfusion, patients eventually recover from anemia. Pancytopenia presents a real problem necessitating a course of intensive therapy.[31] It must be carefully deliberated which of these illnesses should be the target of a new preventive measure that might be implemented. Second, cost-effectiveness must be considered relative to the frequency of TT-B19V. In Japan, more than 5 million people donate blood and approximately 1 million patients receive blood transfusion annually. In such a circumstance, TT-B19V was found to occur at such a low frequency that only seven cases with symptoms were reported during the past 10 years, four of which had an impaired RBC production and one had pancytopenia. These cases were among only 15 reports of suspected TT-B19V, suggesting either that TT-B19V occurrence is very rare or that most clinicians are not aware of TT-B19V. Moreover, most symptoms eventually spontaneously resolve, which might lead to the overlooking or misdiagnosis of the infection. These clinical outcomes of TT-B19V may not support the idea of implementation of a universal donor screening strategy to cope with TT-B19V. However, if more evidence is accumulated showing TT-B19V–related serious illnesses, its implementation may be required in the future.

The universal screening of donated blood for B19V by nucleic acid testing (NAT)-based algorithm is currently carried out in Germany.[27] With the detection limit of 10^5 IU/mL, it is surely contributing to the decrease in not only the viral load in pooled source plasma but also the frequency of seroconversion or symptomatic infection after component transfusion. Our finding of the infectivity of blood components with 10^3 IU/mL viral load suggests that this measure may not completely eliminate TT-B19V cases with serious hematologic disorders. The implementation of NAT screening with a much higher sensitivity for B19V is, however, unlikely because it would impair the current blood program because it would result in the discarding of a considerable number of components.

Another strategy may be feasible in which an indication for the transfusion of B19V-safer blood components is defined and components with negligible B19V infectivity are identified, the strategy currently being recommended in the Netherlands.[32] Our experience with TT-B19V enabled us to define patients at risk of B19V-related serious illnesses; that is, patients with the indication of TT-B19V–safer components, namely, B19V-seronegative patients with an enhanced erythropoiesis or with hereditary RBC disorders having an increased RBC turnover.[3] Seronegative pregnant women are another population at risk because of the high risk of hydrops fetalis.[1] Blood components with no or negligible viral loads will be identified by screening a proportion of the current component inventory using NAT with high sensitivity. To avoid a donation during the NAT window period and early recovery phase after acute infection, components should be selected among donations that show positivity for specific IgG as well as negativity for specific IgM continuously over a long period (e.g., >6 months or 1 year).[32]

Pathogen reduction and/or inactivation is a novel strategy for the prevention of TTIs.[33] It is, however, considered to be difficult in general to mitigate the B19V infectivity of blood components because of the rigid viral capsid of B19V that hinders the entry of the photosensitizer and the extremely high viral load found in blood donors in acute-phase B19V infection.

In conclusion, eight cases of TT-B19V caused by transfusion with B19V-contaminated blood components have been identified through the hemovigilance system. Whether a patient developed a serious B19V-related hematologic disorder as a result of component transfusion depended on the patient's underlying disease state such as an enhanced erythropoiesis, not on the viral concentration of the component transfused.

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CONFLICT OF INTEREST

The authors have no conflict of interest for this article.

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