Precision Treatment for Parvovirus B19 Infection After Hematopoietic Stem Cell Transplantation: a Case Report and Review of the Literature

Xiaohui Zhou

Shenzhen Children's Hospital <https://orcid.org/0000-0002-0427-2164>

Wang Xiaodong

Shenzhen Children's Hospital

Yu Uet

Shenzhen Children's Hospital

Zhang Xiaoling

Shenzhen Children's Hospital

Wang Chunjing

Shenzhen Children's Hospital

Zhang Yu

Shenzhen Children's Hospital

Yang Chunlan

Shenzhen Children's Hospital

Luo Mingjing

Shenzhen Children's Hospital

Li Yue

Shenzhen Children's Hospital

Zhang Qian

Shenzhen Children's Hospital

Lin Zhenhu

Shenzhen Children's Hospital

Jiang Xianping

Shenzhen Children's Hospital

Liu Sixi (✉ tiger647@126.com)

Shenzhen Children's Hospital

Case report

Keywords: parvovirus B19, intravenous immunoglobulin, hematopoietic stem cell transplantation, case report

Posted Date: May 4th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-428338/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Precision treatment for parvovirus B19 infection after hematopoietic stem cell transplantation : a case report and review of the literature

Xiaohui Zhou^{1*}, Xiaodong Wang^{1*}, Uet Yu¹, Xiaoling Zhang¹, Chunjing Wang¹, Yu Zhang¹, Chunlan Yang¹, Mingjing Luo¹, Yue Li¹, Qian Zhang¹, Zhenhu Lin², Xianping Jiang³, Sixi Liu¹

1.Department of Hematology and Oncology, Shenzhen Children's Hospital, 7019 Yitian Road, Futian, Shenzhen, China, 518038

2. Institute for Medical Research, Shenzhen Children's Hospital, Shenzhen, China

3. Department of Pathology, Shenzhen Children's Hospital, Shenzhen, China

*Shared first authors

Corresponding author: Sixi Liu

Email: tiger647@126.com

Tel: +86 189-3869-0206

Key words: parvovirus B19; intravenous immunoglobulin; hematopoietic stem cell transplantation; case report

Abstract

Background: Cytopenia due to parvovirus B19 (PVB19) infection has rarely been reported in recipients of thalassemia major after hematopoietic stem cell transplantation (HSCT). Most of the reported cases were patients undergone solid organ transplantation, especially renal transplant. However, cases of pediatric patients in thalassemia major have rarely been reported.

Case presentation: Here we report a girl that had PVB19-induced anemia while undergoing immunosuppressive therapy after transplant. The patient presented with progressive anemia and had a lowest hemoglobin level of 58 g/L. Bone marrow biopsy showed suppress inhibited erythropoiesis with giant pronormoblasts. Next-generation sequencing of peripheral blood suggested the infection of PVB19. The detection of serum PVB19-DNA using quantitative polymerase chain reaction revealed a viral load of over 1×10^8 copies/ml. The hemoglobin level increased to 113 g/L after six courses of intravenous immunoglobulin (IVIG) therapy. Monitoring of viral load showed PVB19-DNA level remained at a low level for six months before clearance. Pure red cell aplasia was not observed during the treatment period.

Conclusions: Our case suggests that timely and adequately diagnosis and treatment against PVB19 with IVIG is effective and may prevent sequential complications in pediatric HSCT recipients.

Key words: parvovirus B19; intravenous immunoglobulin; hematopoietic stem cell transplantation; case report

Background

Cytopenia is common complication but can cause severe outcomes in patients undergone hematopoietic stem cell transplantation (HSCT). Risk factors associated with the development of post-transplant cytopenia include the use of myelotoxic agents, viral infections, age of donors, human lymphocyte antigen compatibilities, CMV serostatuses of donor and recipient, and stem cell source[1-5]. Pure red cell aplasia (PRCA) caused by PVB19 infection has been sporadically reported in HSCT recipients[6]. However, cases of pediatric patients in thalassemia major have rarely been reported. In this study, we describe a case of girl that developed cytopenia due to PVB19 infection after HSCT.

Case presentation

This is a seven-year-old girl β -thalassemia major that received haploidentical HSCT at Shenzhen Children's Hospital in February 2019. The conditioning regimens consisted of cyclophosphamide (Cy), busulfan (Bu), fludarabine (Flu), thiotepa(TT),rabbit anti-human thymocyte immunoglobulin (ATG). GVHD prophylaxis consisted of post-transplant cyclophosphamide (PTCY), tacrolimus (FK506), and mycophenolate mofetil (MMF), and short-term methotrexate (MTX)[7]. The patient presented with a progressive decrease of hemoglobin level from 110 g/L to 58 g/L within a two-month period starting from 15 weeks after transplantation. Fever was presented intermittent fever for three days, the highest body temperature is 38.8 degrees. The patient did not have graft versus host diseases (GVHDs). Physical examination showed signs of anemia and fatigue, and no other obvious positive signs.

The immunosuppressive reagents are tacrolimus and methylprednisolone, the doses are 1mg q12h and 6mg qd respectively. There was a reduction of reticulocyte count ($3.1 \times 10^9/L$, 0.1% of total red blood cells) and elevated erythropoietin (EPO) level (312.04 mIU/mL, range 1.48 to 31.88 mIU/mL). Quantitative polymerase chain reaction (Q-PCR) examination of CMV, Epstein-Barr virus (EBV)-DNA and hepatitis B virus were under the limit of detection. Autoimmune markers including CD71-positive nucleated red blood cells, CD15-positive granulocyte and CD34-positive primordial cell were not detected. There was a slight decrease of serum folic acid level (5.2ng/ml, range more than 10.6ng/ml). Serum vitamin B12 and iron levels were within the normal range. Bone marrow examination was performed 7 days after the onset of symptoms.

The bone marrow aspiration shows that the number of erythroid cells is low; some of immature red blood cells are present with megablastic changes; giant proerythroblasts appear in the aspirate; megakaryocytes and myeloid cells are normal (Figure 1).

The bone marrow biopsy showed mild hypoplasia of hematopoietic tissue, with a hematopoietic area of sixty percent (Figure 2). Immunohistochemistry examination of the cells revealed positive staining for CD235a(+), CD61(+), Lysozyme(+), MPO(+), PAS(+), EBERs(-). The patient was given folic acid supplementations and reduced the dose of immunosuppressants. However, anemia persisted and the patient developed pancytopenia, with reductions of platelet and leukocyte counts dropping from $188 \times 10^9/L$ to $42 \times 10^9/L$ and $5.25 \times 10^9/L$ to $2.2 \times 10^9/L$, respectively, a month after the presentation of anemia (Figure 3). However, short-tandem-repeat PCR

examinations showed the patient remained full chimerism of donor graft during the disease course hence did not suggest the development of graft failure. Next generation sequencing of peripheral blood was then applied to find unconventional infections that could affect the process of erythropoiesis. An increased copy number of PVB19 was observed. Q-PCR examination of PVB19-DNA in the blood further indicated a high viral load of over 1×10^8 copies/mL. However, serological examination against PVB19 remained negative.

The patient was given intravenous immunoglobulin (IVIG) treatment for three consecutive days four days after the onset of symptoms. There was an increase of reticulocyte count (97.6×10^9 /L) and hemoglobin level (91g/L) a month after the IVIG treatment, accompanied by a significant reduction of blood PVB19-DNA copy numbers (9.6×10^2 copies/mL). Leukocyte and platelet returned to normal 2 weeks after diagnosis and treatment. However, the patient then experienced another course of anemia with reduction of hemoglobin level to 75g/L. This could be due to the reactivation of EBV because plasma EBV-DNA level increased to 2.3×10^3 copies/mL. PVB19-DNA level did not increase at this time (9.7×10^2 copies/mL). She was re-treated with three cycles of IVIG (2.5g per day for 7 day). The patient responded well to IVIG with an increase of hemoglobin level to 107g/L on the next month. PVB19-DNA level was remained a low level (3.33×10^2 copies/mL) for 16 months before clearance. However, the patient's condition was stable and did not have anemia during this period of time.

Discussion

PVB19 is a small, non-enveloped virus that has a diameter of approximately 23–26 nm and contains a linear single-stranded DNA genome of 5.6 kb, flanked by two identical terminal hairpin structures. PVB19 infection causes a wide range of pathological conditions: fifth disease in children, persistent anemia in immunocompromised patients, transient aplastic crises, hydrops fetalis in pregnant women, cardiomyopathy and arthropathy[8-11]. PVB19V infection is more susceptible in the immunocompromised hosts including recipients of HSCT. To understand the etiology and pathogenesis of PVB19V infection and the latest recommendations on the treatment of PVB19V-related diseases in HSCT recipients, we searched for articles written in English that were published between 1990 and December 2019 using “PVB19V infection”, and/or “bone marrow transplantation”, and/or stem cell transplantation, and /or haematopoietic stem cell transplantation on PUBMED. A total of 31 cases from 15 article were found. A summary of these cases and the current case is shown in Table 1.

The time of the onset of PVB19 disease range from 0.03 to 96 months after HSCT.

Rash and cytopenia are the main manifestations of PVB19 infection (26/32 cases)[12-16], followed by other symptoms including arthralgia, malaise, headache, myalgia, and pruritus[17-24]. Four of the 32 patients developed organ failure involving the heart, the lungs, or the kidneys[21, 24],among which three patients also had cytopenia. In addition, cytopenia is more likely to be observed in HSCT recipients 3 months after transplant. In the current case, the key presenting abnormalities of the patient were the anemia and fatigue, and no other obvious

positive signs. Generally, the diagnosis of PVB19 based on clinical symptoms and laboratory examinations. Bone marrow examination is required for diagnosis of PVB19 infection. Patients with erythroid hypoplasia and lack of maturation of proerythroblasts should be considered for further analysis to confirm or exclude PVB19 infection. Serological examinations of PVB19 IgG and IgM, and PCR-based testing of PVB19-DNA are commonly used in the diagnosis of PVB19 infection. Unlike serological examination, PCR-based analysis can be applied to samples collected from almost all sites of infection other than the peripheral blood. However, the sensitivity of either method was not high. Of all of the reported cases, only half of the patients were tested positive by serological examination. Moreover, the use of serological examination may be hampered in HSCT recipients because of the impaired humoral response due to the use of immunosuppressant. PCR-based examination is the method recommended for HSCT recipients, however, may have an even lesser sensitivity. In a cohort of 53 pediatric (of 195) patients HSCT recipients, only 30% of patients were tested positive for PVB19-DNA by qPCR, pre-HSCT (9/53), and at 1 (6/53), 2 (4/53) and 3 months (1/25) post HSCT, respectively[25].

The advancement of Metagenomic Next-Generation Sequencing (mNGS) can detect PVB19-DNA from various types of specimens with high sensitivity and specificity. However, it is recommended to test samples that are collected from the sites of suspected PVB19 infection. PCR can involve numerous individual tests for specifically targeted organisms but may still miss a rare pathogen or use primers containing mismatches to the microbial strain involved, which decreases the

sensitivity of detection[26]. However, conventional testing methods is the limitation in the breadth of pathogens detected, and clinicians are often left with negative results. A chief advantage of mNGS is unbiased sampling, which enables broad identification of known as well as unexpected pathogens or even the discovery of new organisms[27]. Another advantage of mNGS is that it can provide the auxiliary genomic information necessary for evolutionary tracing[28], strain identification [29, 30], and prediction of drug resistance[31]. NGS can provide quantitative or semiquantitative data regarding the concentration of organisms in the sample via the counting of sequenced reads, which is useful for polymicrobial samples or in cases in which more than one pathogen has been implicated in the disease process[32, 33]. Thus, early application of NGS in patients with suspected PVB19 infection can provide timely and adequate guidance for the diagnosis of PVB19 infection. There is no specific antiviral treatment against PVB19. IVIG remains the recommended treatment for patients with PVB19 infection. It is also recommended to reduce the use of immunosuppressive reagents in HSCT recipients with consideration of the presence of other transplant-related complications such as graft versus host diseases. However, the efficacy of IVIG varies between patients and the mechanism behind this is still unclear. In the summary, we observed that 14 out of 25 patients achieved good response to IVIG, with remission of cytopenia and resolution of PVB19 infection related symptoms. Moreover, patients with high levels of viremia tend to have poorer response to IVIG and repeated use of IVIG may be considered for patients that have persistent PVB19 infection and those that are not responded well for the initial

treatment. However, these are based on small number of case reports hence require larger cohort studies for confirmation.

An early study showed that antisera resulting from immunization with baculovirusderived B19V VP1-containing VLP capsids neutralized B19V infection of human erythroid progenitor cells, highlighting that VP1-containing VLPs are applicable as a human vaccine for preventing B19V infection[34, 35]. In recent years, in addition to immunoglobulins, some compounds have been shown to possess inhibitory activity against PVB19. Hydroxyurea is an antiproliferative drug used in the treatment of sickle-cell disease that also possesses inhibitory activity against B19V. The nucleotide analogues Cidofovir and its lipid conjugate Brincidofovir are broad-range antivirals mostly active against dsDNA viruses, which showed an antiviral activity also against B19V. Newly synthesized coumarin derivatives offer possibilities for the development of molecules with antiviral activity[36].

Conclusion

In conclusion, PVB19 infection is rare but can cause life-threatening complications in patients that received HSCT. Post-transplant patients presented with anemia should be carefully evaluated to exclude the PVB19 infection. Multiple approaches including the use of NGS should be considered to enhance the accuracy of detection of PVB19. Timely and adequately treatment of IVIG may prevent severe complications.

Abbreviations

ATG: rabbit anti-human thymocyte immunoglobulin; Bu: busulfan;

Cy: cyclophosphamide; EBV: Epstein-Barr virus; EPO: erythropoietin;
Flu: fludarabine; FK506: tacrolimus; GVHD: graft versus host diseases; HSCT:
hematopoietic stem cell transplantation; IVIG: intravenous immunoglobulin; MMF:
mycophenolate mofetil; MTX: methotrexate; mNGS: Metagenomic Next-Generation
Sequencing; PVB19: parvovirus B19; PTCY: post-transplant cyclophosphamide;
PRCA: Pure red cell aplasia; Q-PCR: Quantitative polymerase chain reaction; TT:
thiotepa

Ethical approval and consent to participate

Ethical approval is not required for this Case report. Written informed consent was
obtained from the patient's parent.

Consent for publication

Written informed consent was obtained from the patient's parent for publication of
this paper and any accompanying images.

Availability of data and materials

Not applicable.

Competing interests

The authors have no competing interests to declare.

Funding

Sanming Project of Medicine in Shenzhen (SZSM201512033), Shenzhen Fund for
Guangdong Provincial High-level Clinical Key Specialties (SZGSP012), Shenzhen
Key Medical Discipline Construction Fund (SZXK034) and Shenzhen Healthcare

Research Project (SZLY2018015) supported the genetic assessment and data analysis for this paper.

Authors' contributions

Both Xiaohui Zhou and Uet Yu drafted this manuscript. Xiaodong Wang provided the concept for this paper. Chunjing Wang Chunlan Yang, Mingjing Luo, Yue Li, Qian Zhang, Xiaoling Zhang, Yu Zhang , Zhenhu Lin and Xianping Jiang contributed to the laboratory examination and data analysis for this paper. Sixi Liu gave critical review to the manuscript.

Acknowledgements

We thank Prof Kuang-Yueh Chiang from the Hospital for Sick Children in Toronto, Canada for the long-time support to help us to provide better care for our pediatric transplant patients.

References:

1. Bittencourt H, Rocha V, Filion A, Ionescu I, Herr AL, Garnier F, Ades L, Esperou H, Devergie A, Ribaud P et al: Granulocyte colony-stimulating factor for poor graft function after allogeneic stem cell transplantation: 3 days of G-CSF identifies long-term responders. Bone Marrow Transplant 2005, 36(5):431-435.
2. Bruno B, Gooley T, Sullivan KM, Davis C, Bensinger WI, Storb R, Nash RA: Secondary failure of platelet recovery after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2001, 7(3):154-162.
3. Peralvo J, Bacigalupo A, Pittaluga PA, Occhini D, Van Lint MT, Frassoni F, Nardelli E, Transino A, Pantarotto M, Marmout AM: Poor graft function associated

238 with graft-versus-host disease after allogeneic marrow transplantation. Bone Marrow
239 Transplant 1987, 2(3):279-285.

240 4. Salzberger B, Bowden RA, Hackman RC, Davis C, Boeckh M: Neutropenia in
241 allogeneic marrow transplant recipients receiving ganciclovir for prevention of
242 cytomegalovirus disease: risk factors and outcome. BLOOD 1997, 90(6):2502-2508.

243 5. Torok-Storb B, Boeckh M, Hoy C, Leisenring W, Myerson D, Gooley T:
244 Association of specific cytomegalovirus genotypes with death from myelosuppression
245 after marrow transplantation. BLOOD 1997, 90(5):2097-2102.

246 6. Karrasch M, Schmidt V, Hammer A, Hochhaus A, Rosee P, Petersen I, Sauerbrei
247 A, Baier M, Sayer HG, Hermann B: Chronic persistent parvovirus B19 bone marrow
248 infection resulting in transfusion-dependent pure red cell aplasia in multiple myeloma
249 after allogeneic haematopoietic stem cell transplantation and severe graft versus
250 host disease. HEMATOLOGY 2017, 22(2):93-98.

251 7. Wang X, Zhang X, Yu U, Wang C, Yang C, Li Y, Li C, Wen F, Li C, Liu S:
252 Co-Transplantation of Haploidentical Stem Cells and a Dose of Unrelated Cord Blood
253 in Pediatric Patients with Thalassemia Major. CELL TRANSPLANT 2021,
254 30:2139987512.

255 8. Cossart YE, Field AM, Cant B, Widdows D: Parvovirus-like particles in human
256 sera. LANCET 1975, 1(7898):72-73.

257 9. Cotmore SF, Agbandje-McKenna M, Chiorini JA, Mukha DV, Pintel DJ, Qiu J,
258 Soderlund-Venermo M, Tattersall P, Tijssen P, Gatherer D et al: The family
259 Parvoviridae. ARCH VIROL 2014, 159(5):1239-1247.

260 10. Qiu J, Soderlund-Venermo M, Young NS: Human Parvoviruses. CLIN
261 MICROBIOL REV 2017, 30(1):43-113.

262 11. Simpson KE, Storch GA, Lee CK, Ward KE, Danon S, Simon CM, Delaney JW,
263 Tong A, Canter CE: High Frequency of Detection by PCR of Viral Nucleic Acid in
264 The Blood of Infants Presenting with Clinical Myocarditis. PEDIATR CARDIOL
265 2016, 37(2):399-404.

266 12. Katoh D, Ochi Y, Hiramoto N, Morita M, Yabushita T, Shimomura Y, Yamashita
267 D, Ono Y, Yoshioka S, Yonetani N et al: Parvovirus B19 infection in adult patients
268 after allogeneic stem cell transplantation: our experience of five cases and literature
269 review. Bone Marrow Transplant 2020, 55(3):653-656.

270 13. Muetherig A, Christopeit M, Muller LP, Grothe W, Weber T, Theurich S, Behre
271 G: Human parvovirus B19 infection with GvHD-like erythema in two allogeneic stem
272 cell transplant recipients. Bone Marrow Transplant 2007, 39(5):315-316.

273 14. Plentz A, Hahn J, Holler E, Jilg W, Modrow S: Long-term parvovirus B19
274 viraemia associated with pure red cell aplasia after allogeneic bone marrow
275 transplantation. J CLIN VIROL 2004, 31(1):16-19.

276 15. Schleuning M, Jager G, Holler E, Hill W, Thomssen C, Denzlinger C, Lorenz T,
277 Ledderose G, Wilmanns W, Kolb HJ: Human parvovirus B19-associated disease in
278 bone marrow transplantation. INFECTION 1999, 27(2):114-117.

279 16. Tsirigotis P, Girkas K, Economopoulou C, Bouchla A, Papanicolaou N,
280 Economopoulou P, Papageorgiou S, Pappa V, Dervenoulas J: Pure Red Cell Aplasia
281 due to B19 Parvovirus Infection after Autologous Stem Cell Transplantation. Case

282 Rep Transplant 2011, 2011:251930.

283 17. Cohen BJ, Beard S, Knowles WA, Ellis JS, Joske D, Goldman JM, Hewitt P,
284 Ward KN: Chronic anemia due to parvovirus B19 infection in a bone marrow
285 transplant patient after platelet transfusion. TRANSFUSION 1997, 37(9):947-952.

286 18. Hayes-Lattin B, Seipel TJ, Gatter K, Heinrich MC, Maziarz RT: Pure red cell
287 aplasia associated with parvovirus B19 infection occurring late after allogeneic bone
288 marrow transplantation. AM J HEMATOL 2004, 75(3):142-145.

289 19. Hsu JW, Czander M, Anders V, Vogelsang G, Brodsky RA: Parvovirus
290 b19-associated pure red cell aplasia in chronic graft-versus-host disease. Br J
291 Haematol 2002, 119(1):280-281.

292 20. Karrasch M, Schmidt V, Hammer A, Hochhaus A, Rosee P, Petersen I, Sauerbrei
293 A, Baier M, Sayer HG, Hermann B: Chronic persistent parvovirus B19 bone marrow
294 infection resulting in transfusion-dependent pure red cell aplasia in multiple myeloma
295 after allogeneic haematopoietic stem cell transplantation and severe graft versus
296 host disease. HEMATOLOGY 2017, 22(2):93-98.

297 21. Klumpen HJ, Petersen EJ, Verdonck LF: Severe multiorgan failure after
298 parvovirus B19 infection in an allogeneic stem cell transplant recipient. Bone Marrow
299 Transplant 2004, 34(5):469-470.

300 22. Soderlund M, Ruutu P, Ruutu T, Asikainen K, Franssila R, Hedman K: Primary
301 and secondary infections by human parvovirus B19 following bone marrow
302 transplantation: characterization by PCR and B-cell molecular immunology. Scand J
303 Infect Dis 1997, 29(2):129-135.

304 23. Wasak-Szulowska E, Grabarczyk P, Rzepecki P: Pure red cell aplasia due to
305 parvovirus B19 infection transmitted probably through hematopoietic stem cell
306 transplantation. *TRANSPL INFECT DIS* 2008, 10(3):201-205.

307 24. Weiland HT, Salimans MM, Fibbe WE, Kluin PM, Cohen BJ: Prolonged
308 parvovirus B19 infection with severe anaemia in a bone marrow transplant patient. *Br*
309 *J Haematol* 1989, 71(2):300.

310 25. Rahiala J, Koskenvuo M, Norja P, Meriluoto M, Toppinen M, Lahtinen A,
311 Vaisanen E, Waris M, Vuorinen T, Saarinen-Pihkala U et al: Human parvoviruses
312 B19, PARV4 and bocavirus in pediatric patients with allogeneic hematopoietic SCT.
313 *Bone Marrow Transplant* 2013, 48(10):1308-1312.

314 26. Wilson MR, Naccache SN, Samayoa E, Biagtan M, Bashir H, Yu G, Salamat SM,
315 Somasekar S, Federman S, Miller S et al: Actionable diagnosis of neuroleptospirosis
316 by next-generation sequencing. *N Engl J Med* 2014, 370(25):2408-2417.

317 27. Chiu CY: Viral pathogen discovery. *CURR OPIN MICROBIOL* 2013,
318 16(4):468-478.

319 28. Gire SK, Goba A, Andersen KG, Sealfon RS, Park DJ, Kanneh L, Jalloh S,
320 Momoh M, Fullah M, Dudas G et al: Genomic surveillance elucidates Ebola virus
321 origin and transmission during the 2014 outbreak. *SCIENCE* 2014,
322 345(6202):1369-1372.

323 29. Deurenberg RH, Bathoorn E, Chlebowicz MA, Couto N, Ferdous M,
324 Garcia-Cobos S, Kooistra-Smid AM, Raangs EC, Rosema S, Veloo AC et al:
325 Application of next generation sequencing in clinical microbiology and infection

326 prevention. J BIOTECHNOL 2017, 243:16-24.

327 30. Salipante SJ, SenGupta DJ, Cummings LA, Land TA, Hoogestraat DR, Cookson
328 BT: Application of whole-genome sequencing for bacterial strain typing in molecular
329 epidemiology. J CLIN MICROBIOL 2015, 53(4):1072-1079.

330 31. Sahoo MK, Lefterova MI, Yamamoto F, Waggoner JJ, Chou S, Holmes SP,
331 Anderson MW, Pinsky BA: Detection of cytomegalovirus drug resistance mutations
332 by next-generation sequencing. J CLIN MICROBIOL 2013, 51(11):3700-3710.

333 32. Salipante SJ, Hoogestraat DR, Abbott AN, SenGupta DJ, Cummings LA,
334 Butler-Wu SM, Stephens K, Cookson BT, Hoffman NG: Coinfection of
335 *Fusobacterium nucleatum* and *Actinomyces israelii* in mastoiditis diagnosed by
336 next-generation DNA sequencing. J CLIN MICROBIOL 2014, 52(5):1789-1792.

337 33. Gu W, Miller S, Chiu CY: Clinical Metagenomic Next-Generation Sequencing
338 for Pathogen Detection. Annu Rev Pathol 2019, 14:319-338.

339 34. Bansal GP, Hatfield JA, Dunn FE, Kramer AA, Brady F, Riggin CH, Collett MS,
340 Yoshimoto K, Kajigaya S, Young NS: Candidate recombinant vaccine for human B19
341 parvovirus. J INFECT DIS 1993, 167(5):1034-1044.

342 35. Kajigaya S, Fujii H, Field A, Anderson S, Rosenfeld S, Anderson LJ, Shimada T,
343 Young NS: Self-assembled B19 parvovirus capsids, produced in a baculovirus system,
344 are antigenically and immunogenically similar to native virions. Proc Natl Acad Sci U
345 S A 1991, 88(11):4646-4650.

346 36. Manaresi E, Gallinella G: Advances in the Development of Antiviral Strategies
347 against Parvovirus B19. Viruses 2019, 11(7).

Figure legends

Figure 1

Morphological examination of the bone marrow aspiration showed (Wright–Giemsa stain,x1000) normal granulopoiesis and megakaryopoiesis(A), but reduced erythropoiesis Grant proerythroblasts with basophilic cytoplasm(B).

Figure 2

Bone marrow biopsy showing mild hypoplasia of hematopoietic tissue by hematoxylin eosin(HE) staining(A,x5 and B,x10).

Figure 3

Correlation of laboratory values (white blood cell, hemoglobin and platelet) and IVIG treatment during diagnosis.

WBC: white blood cell; Hb: hemoglobin; PLT: platelet;

↑:intravenous immunoglobulin

	Number of patients
Patients	
Age (y), median (range)	38(4-59)
Sex, (male/female)	18:12 a
Donor	
Allo-SCT	29
Auto-SCT	2
Hematological disease	
CML	8
AML	7
ALL	6
Lymphoma	3
thalassemia major	1
Others	6
Onset (months) after HSCT,median (range)	4 months, (0.03 ^b -96ms)
0-3 months after HSCT	13
> 3 months after HSCT	18
Detection of PVB19 IgG at onset of disease	
Positive/negative	7 ^c /5
Detection of PVB19 IgM at onset of disease	
Positive/negative	2 ^d /10
Positive PVB19 PCR result at onset of disease	
Positive/negative	29 ^e /0
Symptom	
Rash	15
Cytopenia	14
Organ failure	4
Sample	
Blood	19

Skin	5
Other specimens	3
Organ	
Lung	2
Heart and lung	1
Lung and kindey	1
Treatment	
No treatment	5 ^f
IVIG	18
IVIG and IS reduction	7
Recurrence fo PVB19 infection	
IVIG	22
Outcome	
Alive	24
Dead	7

376 **Table 1**

377 Clinical characteristics of 31 patients with parvovirus B19 disease after allogeneic
378 hematopoietic stem cell transplantation

379 ALL=acute lymphoblastic leukemia

380 AML=acute myeloid leukemia

381 Allo-SCT=allogeneic stem cell transplantation

382 Auto-SCT= autologous stem cell transplantation

383 CML=chronic myeloid leukemia

384 HSCT=hematopoietic stem-cell transplantation

385 IVIG= intravenous immunoglobulin

386 IS=immunosuppressant

387 MPAL=mixed-phenotype acute leukemia;Hgb=hemoglobin

388 PB=peripheral blood

389 PVB19=parvovirus B19

390 a: one case was gender unknown.
391 b: before stem cell transplantation
392 c: one patient was weak positive, seventeen patients PVB19 IgG was not mentioned;
393 one patient was not test
394 d:one patient was weak positive, sixteen patients PVB19 IgG was not mentioned; one
395 patient was not test; one patient was equivocal
396 e: one patient PCR was not mentioned; one patient was not test
397 f: One patient did not mention whether to treat

Figures

Figure 1

Morphological examination of the bone marrow aspiration showed (Wright–Giemsa stain, x1000) normal granulopoiesis and megakaryopoiesis(A), but reduced erythropoiesis and proerythroblasts with basophilic cytoplasm(B).

Figure 2

Bone marrow biopsy showing mild hypoplasia of hematopoietic tissue by hematoxylin eosin(HE) staining(A,x5 and B,x10).

Figure 3

Correlation of laboratory values (white blood cell, hemoglobin and platelet) and IVIG treatment during diagnosis. WBC: white blood cell; Hb: hemoglobin; PLT: platelet; □: intravenous immunoglobulin

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CAREchecklistEnglish2013.pdf](#)