Scientific Research Publishing

International Journal of Clinical Medicine, 2018, 9, 820-825
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Co-Infection of Parvovirus B19, CMV and BK Virus after Renal Transplantation

Hoang Thi Diem Thuy

Department of Nephrology and Endocrinology, Children Hospital 2, Ho Chi Minh City, Vietnam
Email: thuydiemhoanglp@gmail.com

How to cite this paper: Thuy, H.T.D. (2018) Co-Infection of Parvovirus B19, CMV and BK Virus after Renal Transplantation. *International Journal of Clinical Medicine*, **9**, 820-825.
https://doi.org/10.4236/ijcm.2018.911068

Received: September 27, 2018
Accepted: November 27, 2018
Published: November 30, 2018

Abstract

Background: Parvovirus B19 is the agent causing a regenerative anemia in organ transplant recipients, due to their immunodepressive status. The diagnosis is usually confirmed by the presence of virus in the blood and bone marrow via the PCR technique. There is a potential co-infection with other opportunistic viruses in the transplanted patients. However, this population is not routinely screened for Parvovirus B19 infection. *Case Report*: A 14-year-old male patient who received living-donor kidney transplantation developed a severely progressive and aregenerative anemia four weeks later. PCR of Parvovirus B19 was positive from bone marrow aspiration. There were concomittant CMV and BK virus co-infection. The treatment included a reduction of immunosuppressants, intravenous gamma globulin. Valganciclovir has been prescribed for three months that could negativate the CMV blood load. At the end, there was an eradication of parvovirus in the bone marrow. *Conclusion*: This first reported case in Viet Nam which informed that infection with Parvovirus B19 should be investigated in the transplanted population when a regenerative anemia is present. Otherwise, a screening strategy for Parvovirus B19 should also be considered.

Keywords

Parvovirus, Kidney Transplantation, Co-Infection

1. Introduction

Anemia is a common problem after transplantation. The underlying causes are multiple that ranged from regenerative (bleeding, haemolysis) to hypo-regenerative anemia (myelotoxic medication, viral opportunistic infection, graft dysfunction, poor nutritional status) [1]. Parvovirus B19 is a cause of the fifth disease in children, and it can present several clinical scenes: transient age-

nerative anemia crisis, and hydrops fetalis [2]. Severe manifestations due to Parvovirus B19 in transplant recipients have usually been linked to their immunodepressive status [3] [4]. The short and long term outcome of Parvovirus B19 infection in renal transplant recipients is still not appropriately evaluated and there are no guidelines for B19 infection screening in thesepopulation [5]. Identification of the viral DNA in the serum or in the bone marrow by PCR is preferred for diagnosis in the transplanted recipients [6]. In the transplanted recipients, therapy is indicated and composed of the infusions of gamma globulin and reduction of immunosuppressive medication.

We reported a clinical case of a 14-year-old boy who developed a red cell aplastic crisis 2 months after kidney transplantation due to Parvovirus B19, and has completely recovered under treatment.

2. Case Report

This case report described a Vietnamese boy, 14 years old, who presented with end-stage renal failure due to renal hypoplasia on February 2015. He was submitted to continuous ambulatory peritoneal dialysis for five months and then transplanted with his mother kidney on August 2015. The immunosuppression regimen included basiliximab, prednisone, tacrolimus and mycophenolate mofetil. The through level of tacrolimus was targeted at 10 ng/ml. The CMV status was D+R+, PCR CMV negative, which indicated a 6-month-prevention by acyclovir. The donor's B19 status for this recipient at the time of transplanation was unknown.

In October 2015, the patient developed significant progressive anemia, his hemoglobin went down from 12 g/dl before transplantation to 4 g/dl within two months. The patient didn't present any other symptoms and signs. The renal function was in the normal range in the course (blood creatinine was at 0.9 to 1.2 mg/l), without proteinuria and urinary infection. A whole work-up for anemia was undertaken and revealed an aregenerative anemia with low reticulocytes 0.02 M/uL; a normal range for the white lineage and platelets; no finding of blood loss in stool and urine; a normal dosage of haptoglobine, vitamine B12 and ferrous status; absence of erythropoietine antibody. In term of Parvovirus investigation, the serum PCR was negative that prompted us doing bone marrow aspiration. With the multi color real-time PCR technique and taqman probe, we found the presence of Parvovirus B19 in the bone marrow. On the smear, we obtained a poor erythroid lineage, with nuclei chromatin inclusions (**Figure 1**), suggesting inclusions caused by B19. Immediately, the patient was given gamma globulin infusions for five consecutive days of 400 mg/kg/day. Concomitantly, the immunosuppressive regimen was reduced: converting of tacrolimus to cyclosporine, discontinuation of mycophenolate mofetil, adding of everolimus. Simultaneously, the serum PCR CMV showed slightly positive (720 copies). The patient was also received a pre-emptive treatment for CMV infection by valganciclovir for three months.

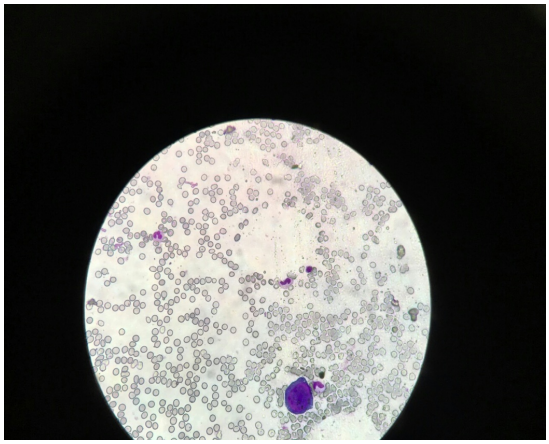

Figure 1. Poor erythroid lineage, with nuclei inclusion (40 magnification).

Four weeks later, parvovirus still was positive in the bone marrow with sustained low hemoglobin at 8 g/dl after two transfusions. His serum CMV was negative but the patient at that time positive the serum BK virus (1092 genom/mL). A transplant biopsy was performed in order to detect BK nephropathy which was normal with negative SV40 staining. The situation has led us to give him a second course of gamma globulin infusion.

Six weeks later, we could eradicate the bone marrow B19 and decrease his serum BK virus (175 genome/ml). The patient then could progressively increase his hemoglobin and reticulocytes. Actually, he is at the second year of transplantation, his hemoglobin was 13 g/dl. He has been routinely screened for rejection because of his minimal immunosuppressive regimen.

At the end of our examination (August 2018), the patient didn't reactivate any opportunistic viral infection with functioning allograft.

3. Discussion

The transmission of Parvovirus B19 is mediated by aerosol droplets containing virus. This infection also can be vertically transmitted, through bone marrow and solid-organ transplants. In normal individual, the viremic phase lasts several days, during which the agenerative anemia occurs [1]. Recovery is related tothe production of antibodies within 10 days later. The prevalence of B19 infection in organ transplant recipients is difficult to estimate because much of the literature consists of case reports rather than monitored cohorts. Cavallo has reported that in the first three months after transplantation, there was 23% (10/48) anemic patients presented active B19 infection [6]. Another longitudinal report has demonstrated an incidence of 1% to 12% renal transplant recipients having B19 infection during the first year, most commonly at the third month [7]. Besides agenerative anemia, other clinical complications included liver dysfunction, fibrosing cholestatic hepatitis, encephalitis, myocarditis and cerebral vasculitis [7].

The humoral immune response has been considered most important for

clearance of virus and for the protection the individual againts re-infection [8]. However, these serologic testing is not contributive for diagnosis because these patients usually have difficulties to rise antiB19. This was the case of our patient. The antibody amount itself is not sufficient to make diagnosis, it may present a dilemma and delay the treatment.

According to many authors, the detection of B19 virus DNA in serum is the best direct marker of active infection [1] [6]. Quantitative PCR assays may be useful in assessing active infection. Unfortunately, at the present time qualitative assay is the only utilized in our country. Even though, we consolidated the diagnosis of parvovirus B19 infection after ruling out other causes of anemia.

The onset of the disease of this case was at the 7th week, which corresponded to the reported cases in the literature. Our patient didn't present any other symptoms such as arthralgia or rash apart his severe anemia. After the reviewed reported cases, the lowest hemoglobine was 4.8 g/dl and the longest duration of anemia was 48 weeks [9]. The reason that prompted us to search for Parvovirus in the bone marrow is the severe aregenerative and unexplainable anemia. In patients who fully presented signs of PVB19 disease but the peripheral blood PCR assay result is negative, the diagnosis may be confirmed by bone marrow PCR [7] [10]. In practice, this was a challenge because anemia after transplantation can be multifactorial and one can delay the exploration of Parvovirus by spending time to search for other causes of anemia. Two main therapeutic options have been proposed once the diagnosis is established: immunosuppressive reduction and gamma globulin infusions. There also was a debate on what immunosuppressors should be withdrawn: antimetabolite or tacrolimus. Tacrolimus was usually switched to cyclosporine in many reports. Most authors agreed with the use of commercial gamma globulin, that help to eradicate the virus due to its neutralizing activity [11] [12]. There has been significant debate over the utility of low (0.25 g/kg/body weight) versus high dose regimens. Lutsliedfield failed to eradicate the virus with the dose of 0.25 g/kg/day for three days [10]. In our case, the dose of gamma globulin was not low in total but we needed a second course to stabilize the anemia. The presence of acquired B19 antibodies still be lower in children than in adults, that might explain multiple doses of gamma globulin needed to eradicate the virus. Bertoni has reported that the incidence of IgG positive was only 50% in children under 15 year-old versus 90% in elderly [13]. A case report in a 15-year-old boy has demonstrated that severe anemia due to Parvorirus B19 only subsided 24 months, after three courses of gamma globulin [14]. Choi and Hiroshi also reported cases of severe anemia due to Parvovirus infection that needed more than one course of gamma globulin and took several weeks to subside [9] [14].

The co-infection of polyoma virus and CMV has been recently reported in kidney transplant recipients [15] [16] [17] but there is very scarce data on CMV co-infection with Parvovirus. This incidence was estimated of 1% [7]. Many opportunistic infections result from reactivation of latent state in the host or from

the graft. Subsequently, the expression of antigen to the APC provoking from the virus can lead to graft rejection. Regarding the CMV co-infection in our case, mycophenolate mofetil was discontinued and replaced by everolimus. The rationale for everolimus use is the risk of allograft rejection in Parvovirus infection was 10%, particularly in children [1] [7]. Additionally, everolimus use also resided at its antiviral potential in the setting of CMV and BK virus co-infection. However, everolimus associated with valganciclovir put this patient in higher risk of myelosuppresion, needing closed vigilance. At the end of the following, the load of virus was all ameliorated. Regarding BK virus infection, there is until now no precised protocole for children, a 30% reduction in calcineurine-inhibitor dosing, 50% reduction in antiproliferative drug dosing has been a common practice [18]. On this patient, we holded a trough level of cyclosporine at 80 - 100 ng/ml and everolimus at 8 ng/ml.

Although there are until now no consensus for screening and treatment for parvovirus B19 infection in organ transplant recipients, it should be judicious to search for Parvovirus B19 in anemic patients. According to Egbuna, the high risk recipients to be screened include the recipientswho have had antibody induction therapy, have a history of treatment for acute rejections, or have other viral infections such as CMV and EBV infections [18].

4. Conclusion

This is a first report on Parvovirus B19 infection in the pediatric transplants in Viet Nam. Our case illustrated that we should look for this virus in our frame work for anemia after transplantation. The first line treatment is reduction in immunosuppression and gamma globulin infusions. A strict monitoring for co-infection of other virus as well as allograft rejection should be considered.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Waldman, M. and Kopp, J.B. (2007) Parvovirus B19 and the Kidney. *Clinical Journal of the American Society of Nephrology,* **2**, 47-56. https://doi.org/10.2215/CJN.01060307

[2] Jordan, J.A. (1996) Identification of Human Parvovirus B19 Infection in Idiopathic Nonimmune Hydrops Fetalis. *American Journal of Obstetrics and Gynecology*, **174**, 37-42. https://doi.org/10.1016/S0002-9378(96)70370-8

[3] Zilinska, Z., Chrastina, M., Breza, J. and Drakulova, M. (1989) Parvovirus B19 Infection—The Cause of Severe Anaemia after Renal Transplantation. *Microbial Pathogenesis*, **7**, 319-327.

[4] Zolnourian, Z.R., Curran, M.D., Rima, B.K., Coyle, P.V., O'Neill, H.J. and Middleton, D. (2000) Parvovirus B19 in Kidney Transplant Patients. *Transplantation*, **69**, 2198-2202. https://doi.org/10.1097/00007890-200005270-00043

[5] Kasiske, B.L., Zeier, M.G., Chapman, J.R., Craig, J.C., Ekberg, H., *et al.* (2010) KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients: A Summary. *Kidney International*, **77**, 299-311. https://doi.org/10.1038/ki.2009.377

[6] Cavallo, R., Merlino, C., Re, D., Bollero, C., Bergallo, M., Lembo, D., Musso, T., Leonardi, G., Segoloni, G.P. and Ponzi, A.N. (2003) B19 Virus Infection in Renal Transplant Recipients. *Journal of Clinical Virology*, **26**, 361-368. https://doi.org/10.1016/S1386-6532(02)00104-X

[7] Eid, A.J., Brown, R.A., Patel, R. and Razonable, R.R. (2006) Parvovirus B19 Infection after Transplantation: A Review of 98 Cases. *Clinical Infectious Diseases*, **43**, 40-48. https://doi.org/10.1086/504812

[8] Moudgil, A., Shidban, H., Nast, C.C., Bagga, A., Aswad, S., Graham, S.L., Mendez, R. and Jordan, S.C. (1997) Parvovirus B19 Infection-Related Complication in Renal Transplant Recipients: Treatment with Intravenous Immunoglobulin. *Transplantation*, **64**, 1847-1850. https://doi.org/10.1097/00007890-199712270-00037

[9] Choi, S.H., Chang, S.P., Won, J.C., Lee, J.S., Chi, H.S., Yang, W.S. and Park, S.K. (2002) A Case of Persistent Anemia in a Renal Transplant Recipient: Association with Parvovirus B19 Infection. *Scandinavian Journal of Infectious Diseases*, **34**, 71-75. https://doi.org/10.1080/003655402753395247

[10] Liefeldt, L., Buhl, M., Schweickert, B., Engelmann, E., Sezer, O., Laschinski, P., Preuschof, L. and Neumayer, H.-H. (2002) Eradication of Parvovirus B19 Infection after Renal Transplantation Requires Reduction of Immunosuppression and High-Dose Immunoglobin Therapy. *Nephrology Dialysis Transplantation*, **17**, 1840-1842. https://doi.org/10.1093/ndt/17.10.1840

[11] Modrow, S. and Dorsch, S. (2002) Antibody Responses in Parvovirus B19 Infected Patients. *Pathologie Biologie* (*Paris*), **50**, 326-331. https://doi.org/10.1016/S0369-8114(02)00302-4

[12] Shen, Q., Xu, H., Cao, Q., Zhou, L.J., Xu, J., Fang, X.Y. and Ge, J. (2011) Long-Term Remission of Recurrent Severe Anemia as a Result of Parvovirus B19 Infection in a Pediatric Renal Transplantation Recipient. *Pediatric Transplantation*, **15**, E76-E79. https://doi.org/10.1111/j.1399-3046.2010.01291.x

[13] Bertoni, E., Rosati, A., Zanazzi, M., Azzi, A., Zakrzewska, K., Guidi, S., Fanci, R. and Salvadori, M. (1997) Aplastic Anemia Due to B19 Parvovirus Infection in Cadaveric Renal Transplant Recipients: An Underestimated Infectious Disease in the Immunocompromised Host. *Journal of Nephrology*, **13**, 17-24.

[14] Chisaka, H., Morita, E., Yaegashi, N. and Sugamura, K. (2003) Parvovirus B19 and the Pathogenesis of Anaemia. *Reviews in Medical Virology*, **13**, 347-359. https://doi.org/10.1002/rmv.395

[15] Cukuranovic, J., Ugrenovic, S., Jovanovic, I., Visnjic, M. and Stefanovic, V. (2012) Viral Infection in Renal Transplant Recipients. *The Scientific World Journal*, **2012**, Article ID: 820621. https://doi.org/10.1100/2012/820621

[16] Keung, Y.K., Chuahirun, T. and Wesson, D. (1999) Concomitant Parvovirus B19 and Cytomegalovirus Infections after Living-Related Renal Transplantation. *Nephrology Dialysis Transplantation*, **14**, 469-471. https://doi.org/10.1093/ndt/14.2.469

[17] Acott, P.D. and Hirsch, H.H. (2007) BK Virus Infection, Replication, and Diseases in Pediatric Kidney Transplantation. *Pediatric Nephrology*, **22**, 1243-1250. https://doi.org/10.1007/s00467-007-0462-x

[18] Egbuna, O., Zand, M.S., Arbini, A., Menegus, M. and Taylor, J. (2005) A Cluster of Parvovirus B19 Infections in Renal Transplant Recipients: A Prospective case series and review of Literature. *American Journal of Transplantation*, **6**, 225-231. https://doi.org/10.1111/j.1600-6143.2005.01139.x