

Case Report

Human Herpes Virus-6 Encephalitis Following Autologous Blood and Marrow Transplant

Jacques Mario Azzi^{1,*}, Doyun Park^{1,2}, Maher Abdul-Hay^{1,2}, Kelli Cole², Frank Cirrone², Maxim Kreditor¹, A. Samer Al-Homsi^{1,2}

¹Department of Medicine, New York University School of Medicine, New York, NY

²Blood and Marrow Transplantation, New York University Medical Center, New York, NY

ARTICLE INFO

Article History

Received 03 Sep 2019
Accepted 21 Nov 2019

Keywords

Encephalitis
Bone marrow transplant
Human herpes virus 6
Multiple myeloma

ABSTRACT

Human herpesvirus-6 (HHV-6) is a highly prevalent virus that establishes lifelong latency in human hosts. Symptomatic HHV-6 reactivation rarely occurs in immunocompetent individuals and is best described in immunosuppressed patients such as recipients of bone marrow transplants (BMT). In that setting, HHV-6 reactivation has been associated with fever, rash, pneumonitis, encephalitis, and delayed engraftment. While these complications are well documented in allogeneic transplant, the clinical impact of such reactivation is not well known in autologous BMT. We described a case of HHV-6-associated encephalitis in a previously heavily treated patient with multiple myeloma (MM) following a second autologous BMT, and discuss the need for clinicians to be aware of the potential clinical impact of HHV-6 following autologous BMT in the era of immunomodulatory agents.

© 2019 International Academy for Clinical Hematology. Publishing services by Atlantis Press International B.V. This is an open access article distributed under the CC BY-NC 4.0 license (<http://creativecommons.org/licenses/by-nc/4.0/>).

1. INTRODUCTION

Human herpesvirus-6 (HHV-6) is a ubiquitous lymphotropic virus with a preference for cluster of differentiation 4 positive (CD4+) T cells, which establishes lifelong latency via integration of its genome into host telomeres [1–3]. In the USA and UK, 97%–100% of primary infections are due to HHV-6 type B, which infects almost all humans by age 3, classically manifesting as a self-limited febrile illness which can include fever and skin rash [4]. After latency, symptomatic reactivation of HHV-6 is best described in the setting of iatrogenic immunosuppression as seen in recipients of allogeneic blood and marrow transplants (BMT) [5,6]. In fact, HHV-6 reactivation is encountered in 36%–45% of allogeneic BMT recipients, and up to 90% of umbilical cord blood transplant patients [7–9]. Active infection in allogeneic BMT has been associated with fever, skin rash, interstitial pneumonitis and delayed engraftment, with HHV-6 associated encephalitis being the most devastating complication [10–13].

The clinical impact of HHV-6 reactivation in autologous BMT patients remains unclear. However, the incidence of viral reactivation has been shown to be comparable to that in allogeneic BMT recipients in a number of studies [14–17]. A recent prospective study published by Balsat *et al.* showed a cumulative incidence of

HHV-6 reactivation rate of 19% by day +40 following autologous BMT [18].

We report an unusual case of encephalitis attributed to HHV-6 in a patient with multiple myeloma (MM) who underwent autologous BMT. This is the second reported case of HHV-6 encephalitis after autologous BMT [19].

2. CASE DESCRIPTION

A 67-year-old female was re-admitted on day +22 following autologous BMT for MM. The patient was noted to have a three-day duration of increased confusion, agitation, and unsteady gait. The patient's MM had been diagnosed four years prior to her current admission. Her previous therapy included induction with 6 cycles of lenalidomide, bortezomib, and dexamethasone followed by high dose melphalan and autologous BMT. Due to progressive disease, she received multiple lines of salvage therapies including lenalidomide, elotuzumab, and dexamethasone, bortezomib and daratumumab, and carfilzomib, pomalidomide, and dexamethasone. After documented response to the last combination, she underwent consolidation therapy with a second autologous BMT following conditioning with melphalan 200 mg/m². Her transplant course was complicated by recurrent fevers at the time of engraftment with the first febrile episode starting on day +9. Extensive work-up was unremarkable, with the exception of HHV-6 type B reactivation, with a viral load of 82,700 copies/mL. Her fever ultimately resolved spontaneously, and the patient remained without complaint until presentation, per above.

*Corresponding author. Postal address: 550 1st Avenue, New York, NY 10016. Email: Jacques.Azzi@nyulangone.org
Peer review under responsibility of the International Academy for Clinical Hematology

Upon admission, HHV-6 encephalitis was suspected. Her serum HHV-6 viral load was 179,000 copies/mL. Her absolute lymphocyte count was $1 \times 10^9/L$. Lymphocyte subsets testing was not done. An MRI of the brain showed no parenchymal or leptomeningeal abnormalities. Cerebrospinal fluid (CSF) demonstrated normal glucose, elevated protein at 63 mg/dL (reference range: 15–40), and increased cell count at $43/mm^3$ (reference range: 0–5), including 95% lymphocytes. Cytology was negative for malignant cells. CSF bacterial and fungal cultures were negative. A polymerase chain reaction (PCR) panel was negative for Herpes simplex virus (HSV), Epstein-barr virus (EBV), cytomegalovirus (CMV), and John Cunningham virus (JC) but positive for HHV-6. Based on peripheral eosinophilia and skin biopsy, the patient was also diagnosed with drug reaction with eosinophilia and systemic symptoms (DRESS). The patient was initially treated with foscarnet for a total of 21 days, followed by a course of valganciclovir. She exhibited gradual clinical improvement and progressively returned to her baseline. Concomitantly, her HHV-6 viral load dropped from 179,000 to 6,400 copies/mL at completion of the antiviral treatment. She remained well until she received maintenance therapy with carfilzomib, pomalidomide and steroids due to persistent disease. This resulted in fever and increase in her viral load. Her anti-myeloma treatment was discontinued, and her symptoms subsided without additional antiviral therapy.

3. DISCUSSION

Since HHV-6 was first described in 1986 in 6 patients with lymphoproliferative disorders [20], its pathogenic role has been progressively elucidated, notably via reactivation in the setting of immune dysfunction such as solid organ transplantation, allogeneic BMT, and acquired immune deficiency syndrome (AIDS) [5,21]. In allogeneic BMT, HHV-6 reactivation is observed in 47%–72% of recipients [11] and can cause a broad spectrum of clinical manifestations such as fever, skin rash, myelosuppression and pneumonitis. The most severe consequence of HHV-6 infection is encephalitis, which occurs at a rate of 0%–11.6% in allogeneic BMT and up to 21.4% in cord blood transplants, typically 3–4 weeks post-transplant [10,12,13,22]. Allogeneic BMT recipients receiving myeloablative conditioning, and those receiving grafts from unrelated donors, human leukocyte antigen (HLA) mismatched donors, and umbilical cord donors are at high risk of HHV-6 reactivation and, particularly, HHV-6 encephalitis [9,13]. One study concluded that in 1,344 cases of allogeneic BMT, 1.4% of patients developed encephalitis attributed to HHV-6. The majority of cases were recipients of umbilical cord transplants [23]. Similarly, in another prospective study of 230 allogeneic BMT recipients, 3% of patients developed HHV-6 encephalitis, with more cases detected in umbilical cord recipients compared to recipients of adult donors (7.9% versus 1.2%) [13].

The clinical impact of HHV-6 reactivation in autologous BMT patients is less well defined and is rarely reported, when compared with the knowledge in allogeneic BMT patients. This is likely due to the paucity of cases, and the traditional thinking that autografted patients experience less immunosuppression than allogeneic recipients. In addition, the limited studies in autografted patients have alluded to the benign course of HHV-6 reactivation in these recipients [15,24,25]. Many of these studies were conducted prior to the

widespread use of novel immunomodulator agents in MM, such as lenalidomide, pomalidomide, and bortezomib, in addition to targeted therapies such as daratumumab and elotuzumab. The incorporation of novel therapies in the treatment of both MM and lymphoma may be rendering this patient population more susceptible to infectious complications. Both pomalidomide and lenalidomide have been shown to induce the activation of cytotoxic T cells and to enhance the cytotoxicity of natural killer (NK) cells, resulting in an increased frequency of mature regulatory T cells [26]. Bortezomib therapy causes a decrease in NK and CD8+ cells, dendritic cell dysfunction, and selective Th1 cell depletion [27]. This has a known negative impact on the immune system, mainly by decreasing the CD4+ and CD8+ T cell population, as well as selective exhaustion of T helper and dendritic cells. Thirteen percent of patients with MM treated with bortezomib develop *Herpes zoster* infection or reactivation [28,29]. In a series of 62 MM patients who received autologous BMT, Horowitz *et al.*, reported that at least one third (10 patients) of unexplained post-engraftment fevers were due to HHV-6 reactivation [17]. All those patients had received bortezomib or thalidomide pre-transplant. While most of them did not receive any HHV-6 directed therapy and had relatively benign courses, our patient developed encephalitis and required treatment with antiviral therapy. This could be due to the fact that our patient received a longer course of immunomodulatory treatment and two transplants. Lymphocyte subset analysis was not done in our case. Future studies should determine whether such testing is of value in assessing the risk of HHV-6 activation following treatment with immunomodulatory agents.

When testing for HHV-6 reactivation by PCR, clinicians should be aware that, in some patients, the virus is acquired through vertical transmission, a rare entity known as chromosomal integration, where the virus is integrated into the telomere of every chromosome. Typically, these patients have persistently high viral load when whole blood but not plasma is examined. Though these patients are most often asymptomatic, in rare instances the virus is able to excise itself from the telomere and cause active infection [2].

Ours is only the second described case of HHV-6 encephalitis following autologous BMT. We believe that in the era of immunomodulatory therapy, transplant clinicians should include testing for HHV-6 in patients with unexplained fever following autologous BMT. Clinicians should also include HHV-6 encephalitis in the differential diagnosis in heavily pretreated patients with MM presenting with neurologic findings. Larger prospective studies are needed to determine which patients are at risk of HHV-6 reactivation, and within this group, which patients are at risk of developing complications requiring directed antiviral therapy.

CONFLICT OF INTEREST

The authors report no financial disclosures relevant to the manuscript.

AUTHORS' CONTRIBUTIONS

All authors take full responsibility for the information provided in the manuscript and agree to the conditions noted in the Authorship Agreement Form.

REFERENCES

- [1] Agut, H, Bonnafous, P, Gautheret-Dejean, A. Laboratory and clinical aspects of human herpesvirus 6 infections. *Clin Microbiol Rev* 2015;28;313–35.
- [2] Pantry, SN, Medveczky, PG. Latency, integration, and reactivation of human herpesvirus-6. *Viruses* 2017;9;1–12.
- [3] Lusso, P, Markham, PD, Tschachler, E, di Marzo Veronese, F, Salahuddin, F, Ablashi, SZ, Ablashi, DV, et al. In vitro cellular tropism of human B-lymphotropic virus (human herpesvirus-6). *J Exp Med* 1988;167;1659–70.
- [4] Ablashi, D, Agut, H, Alvarez-Lafuente, R, Clark, DA, Dewhurst, S, DiLuca, D, et al. Classification of HHV-6A and HHV-6B as distinct viruses. *Arch Virol* 2014;159;863–70.
- [5] Hentrich, M, Oruzio, D, Jager, G, Schlemmer, M, Schleuning, M, Schiel, X, et al. Impact of human herpesvirus-6 after haematopoietic stem cell transplantation. *Br J Haematol* 2005;128;66–72.
- [6] Perissinotti, AJ, Gulbis, A, Shpall, EJ, Howell, J. Characterizing human herpes virus 6 following hematopoietic stem cell transplantation. *J Oncol Pharm Pract* 2015;21;85–92.
- [7] Chevallier, P, Hebia-Fellah, I, Planche, L, Guillaume, T, Bressolette-Bodin, C, Coste-Burel, M, et al. Human herpes virus 6 infection is a hallmark of cord blood transplant in adults and may participate to delayed engraftment: a comparison with matched unrelated donors as stem cell source. *Bone Marrow Transplant* 2010;45;1204–11.
- [8] Kadakia, MP, Rybka, WB, Stewart, JA, Patton, JL, Stamey, FR, Elsayy, M, et al. Human herpesvirus 6: infection and disease following autologous and allogeneic bone marrow transplantation. *Blood* 1996;87;5341–54.
- [9] Yamane, A, Mori, T, Suzuki, S, Mihara, A, Yamazaki, R, Aisa, Y, et al. Risk factors for developing human herpesvirus 6 (HHV-6) reactivation after allogeneic hematopoietic stem cell transplantation and its association with central nervous system disorders. *Biol Blood Marrow Transplant* 2007;13;100–6.
- [10] Yoshikawa, T, Asano, Y, Ihira, M, Suzuki, K, Ohashi, M, Suga, S, et al. Human herpesvirus 6 viremia in bone marrow transplant recipients: clinical features and risk factors. *J Infect Dis* 2002;185;847–53.
- [11] de Pagter, PJ, Schuurman, R, Meijer, E, van Baarle, D, Sanders, EA, Boelens, JJ. Human herpesvirus type 6 reactivation after haematopoietic stem cell transplantation. *J Clin Virol* 2008;43;361–6.
- [12] Zerr, DM, Corey, L, Kim, HW, Huang, ML, Nguy, L, Boeckh, M. Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. *Clin Infect Dis* 2005;40;932–40.
- [13] Ogata, M, Satou, T, Kadota, J, Saito, N, Yoshida, T, Okumura, H, et al. Human herpesvirus 6 (HHV-6) reactivation and HHV-6 encephalitis after allogeneic hematopoietic cell transplantation: a multicenter, prospective study. *Clin Infect Dis* 2013;57;671–81.
- [14] Inazawa, N, Hori, T, Nojima, M, Saito, M, Igarashi, K, Yamamoto, M, et al. Virus reactivations after autologous hematopoietic stem cell transplantation detected by multiplex PCR assay. *J Med Virol* 2017;89;358–62.
- [15] Moschetti, D, Galieni, P, Valensin, PE, Laszlo, D, Scalia, G, Tozzi, M, et al. Human herpesvirus 6 infection in autologous bone marrow transplant recipients: a prospective study. *J Med Virol* 2000;60;39–42.
- [16] Wilborn, F, Brinkmann, V, Schmidt, CA, Neipel, F, Gelderblom, H, Siegert, W. Herpesvirus type 6 in patients undergoing bone marrow transplantation: serologic features and detection by polymerase chain reaction. *Blood* 1994;83;3052–8.
- [17] Horowitz, N, Oren, I, Lavi, N, Zuckerman, T, Benyamini, N, Kra-Oz, Z, et al. New rising infection: human herpesvirus 6 is frequent in myeloma patients undergoing autologous stem cell transplantation after induction therapy with bortezomib. *Bone Marrow Res* 2012;2012;409765.
- [18] Balsat, M, Pillet, S, Tavernier, E, Cacheux, V, Escuret, V, Molucon-Chabrot, C, et al. Human herpesvirus 6 infection after autologous stem cell transplantation: a multicenter prospective study in adult patients. *J Infect* 2019;79;36–42.
- [19] Bommer, M, Pauls, S, Greiner, J. Challenging complications of treatment—human herpes virus 6 encephalitis and pneumonitis in a patient undergoing autologous stem cell transplantation for relapsed Hodgkin's disease: a case report. *Virol J* 2009;6;111.
- [20] Salahuddin, SZ, Ablashi, DV, Markham, PD, Josephs, SF, Sturzenegger, S, Kaplan, M, et al. Isolation of a new virus, HBLV, in patients with lymphoproliferative disorders. *Science* 1986; 234;596–601.
- [21] Razonable, RR, Lautenschlager, I. Impact of human herpes virus 6 in liver transplantation. *World J Hepatol* 2010;2;345–53.
- [22] El-Jawahri, AR, Schaefer, PW, El Khoury, JB, Martinez-Lage, M. Case 5-2018: a 63-year-old man with confusion after stem-cell transplantation. *N Engl J Med* 2018;378;659–69.
- [23] Hill, JA, Koo, S, Guzman Suarez, BB, Ho, VT, Cutler, C, Koreth, J, et al. Cord-blood hematopoietic stem cell transplant confers an increased risk for human herpesvirus-6-associated acute limbic encephalitis: a cohort analysis. *Biol Blood Marrow Transplant* 2012;18;1638–48.
- [24] Imbert-Marcille, BM, Tang, XW, Lepelletier, D, Besse, B, Moreau, P, Billaudel, S, et al. Human herpesvirus 6 infection after autologous or allogeneic stem cell transplantation: a single-center prospective longitudinal study of 92 patients. *Clin Infect Dis* 2000;31;881–6.
- [25] Galieni, P, Moschetti, D, Donati, D, Tozzi, M, Valensin, PE, Lauria, F. Long-term follow-up of human herpes virus 6 infection in autologous bone marrow transplant recipients. *Haematologica* 2001;86;782–3.
- [26] Kotla, V, Goel, S, Nischal, S, Heuck, C, Vivek, K, Das, B, et al. Mechanism of action of lenalidomide in hematological malignancies. *J Hematol Oncol* 2009;2;36.
- [27] Nencioni, A, Garuti, A, Schwarzenberg, K, Cirmena, G, Dal Bello, G, Rocco, I, et al. Proteasome inhibitor-induced apoptosis in human monocyte-derived dendritic cells. *Eur J Immunol* 2006;36;681–9.
- [28] Kim, JW, Min, CK, Mun, YC, Park, Y, Kim, BS, Nam, SH, et al. Varicella-zoster virus-specific cell-mediated immunity and herpes zoster development in multiple myeloma patients receiving bortezomib- or thalidomide-based chemotherapy. *J Clin Virol* 2015;73;64–9.
- [29] Onaka, T, Yonezawa, A. Herpes zoster duplex bilateralis in bortezomib-based chemotherapy. *Blood Res* 2016;51;155.