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Case Report
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Fatal Human Herpesvirus-6 Infection Following CD45RA T Cell-Depleted Fully Matched Unrelated Donor Hematopoietic Stem Cell Transplantation

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Abstract

T cell-depleted grafts may increase fungal and viral infections following allogeneic Hematopoietic Stem Cell Transplantation (HSCT). A severe human herpesvirus-6 infection was detected after a CD45RA T cell-depleted fully matched unrelated donor HSCT for an adult patient with B-cell acute lymphoblastic leukemia with t(9;22) (q34.1;q11.2). Despite combined treatment with ganciclovir and foscarnet, a rapid multi-organ failure set in and was fatal.

Keywords: Human herpesvirus-6; CD45 RA T-cell depletion; Matched unrelated donor; Hematopoietic stem cell transplantation; B-cell acute lymphoblastic leukemia

Introduction

Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) is a curative therapy in adult and pediatric patients with high-risk hematologic malignancies [1]. However, despite a high percentage of graft success [2], the development of Graft Versus Host Disease (GVHD) [3] and the appearance of serious infections secondary to delayed immune reconstitution continue to be the leading causes of morbidity and mortality in this type of therapeutic procedure [4,5].

The development of graft manipulation techniques, such as T-cell depletion, has significantly reduced the risk of acute and chronic GVHD in the absence of prophylactic post-transplant immunosuppression [6-10]. However, they can cause graft failure and delayed immune reconstitution, favoring the appearance of potentially fatal opportunistic infections, especially fungal and viral infections [10].

Infection or reactivation by Human Herpesvirus-6 (HHV-6) following HSCT is increasingly observed, appearing in the first 2 to 4 weeks after HSCT [11]. Systemic involvement can lead to complications such as exanthema, kidney and liver failure, encephalitis, graft failure or the development of GVHD [12-15]. Although HHV-6 infection can be life-threatening, there is a lack of strategy in prophylaxis, early detection, and monitoring of the virus. Moreover, there is no established treatment for HHV-6 infection, although foscarnet or ganciclovir have been recommended for the treatment of encephalitis [11].

A case of acute HHV-6 infection following a fully matched unrelated donor myeloablative HSCT with a CD45RA T cell-depletion graft is presented. Despite close monitoring by PCR and early treatment with combined foscarnet and ganciclovir, a rapid and fatal evolution was observed.

Case Presentation

A 42-year-old Caucasian male with no relevant personal medical history was diagnosed with B-cell acute lymphoblastic leukemia with t(9;22) (q34.1;q11.2) in June 2022. He received intensive induction chemotherapy with vincristine, daunorubicin, prednisone plus imatinib (600 mg daily) and standard intrathecal chemotherapy, achieving morphologic complete remission. Afterwards, consolidation chemotherapy was given according to the PETHEMA LAL Ph+ 2008 protocol for patients under 55 years of age [16]. Complete remission was maintained but minimal residual disease (0.04% *BCR-ABL/ABL*) was detected. Due to the high risk of disease progression an HSCT was indicated, and an unrelated search initiated, as the patient did not have an HLA matched family donor.

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A fully matched unrelated donor peripheral blood HSCT conditioned with total body irradiation (12 Gy) and cyclophosphamide (60 mg/Kg for two consecutive days) was performed. For GVHD prophylaxis, a CD34-positive selection followed by a CD45RA naïve T cell-depletion was planned. Therefore, 8.71×10^6 CD34+ cells/kg were infused followed by an infusion of 1×10^6 /kg CD45+ depleted CD3+ cells. The total number of residual CD3+CD45RA+ cells infused was 5.4×10^3/kg. The patient also received prophylactic antimicrobial treatment with rifaximin, trimethoprim-sulfamethoxazole, acyclovir, letermovir, and fluconazole.

Early post-transplant complications were grade 4 mucositis requiring intravenous morphine and total parenteral nutrition and radiodermatitis on face, neck, armpits, and groin, successfully treated with topical silver sulfadiazine. On day +3 post-transplant neutropenic fever of unknown origin appeared and empirical progressive antibiotic treatment with meropenem was started. Fever without microbiological documentation persisted and amikacin, vancomycin and posaconazole were added to the empirical antibiotic treatment. On day +12 post-transplant, an erythematous, non-pruritic skin rash appeared on the arms, legs, and neckline. A skin biopsy was negative for GVHD, implant syndrome or infection. However, all the symptoms subsided with prednisone 1 mg/kg/bid. Granulocyte engraftment (>0.5×10^9/L, absolute neutrophil count) was achieved at day +11 and platelet engraftment (>20×10^9/L, without transfusions) by day +8. An early complete donor chimerism was observed on day +15.

On day +13 post-transplant a new onset of persistent fever was detected in parallel with elevated acute phase reactants and progressive cytopenia's. Extensive and repeated blood, urine and fecal microbiological tests and imaging studies were performed but they were all negative ((bacterial and fungal cultures, multiviral PCR testing including HHV-6 and high-resolution turaco-abdominal scans). However, only three days later, a new PCR for HHV-6 was positive with 164,872 copies/mL. On day +19 post-transplant a bone marrow study detected hemophagocytosis and ruled out leukemic recurrence. Due to the concomitant presence of hypertriglyceridemia (1,241 mg/dl), increased LDH (14,847 IU/L), elevated ferritin (356,000 mg/dl), thrombocytopenia (36×10^9/L) and monocytosis (11.3×10^9/L), a diagnosis of hemophagocytic lymphohistiocytosis secondary to acute infection by HHV-6 was made. Treatment with intravenous immunoglobulins (30 g/d, two days), foscarnet (90 mg/Kg/bid, ganciclovir (5 mg/kg/d), etoposide (100 mg) and anakinra (200 mg/day) was started. Dexamethasone was not included due to the viral infection. After administration of etoposide, the patient developed an acute renal failure showing creatinine 4.5 mg/dl, hyperuricemia (12.7 mg/dl), hyperphosphatemia (7.3 mg/dl), hyperkalemia (5.4 mmol/L) and hypocalcemia (5.7 mg/dl) and requiring rasburicase and intensive fluid therapy with electrolytes balance. Despite treatment, the HHV-6 infection reached 5,811,644 copies/ml and the patient worsened clinically and analytically, developing SIADH with hyponatremia (119 mmol/L), Disseminated Intravascular Coagulation (DIC) (fibrinogen of 73 mg/dl) and a generalized hemorrhagic rash. Two days later, the HHV-6 levels subsided (1,858,396 copies/ml), but the patient was admitted to the intensive care unit due to multi-organ failure (renal, hepatic, pulmonary, neurologic, DIC) and died on day +25 post-transplant with a concomitant septic shock from *Enterococcus faecium*.

Discussion

Transplant related mortality following allogeneic HSCT has been significantly reduced due to better donor selection and improvement in transplant techniques [17]. To prevent the onset of GVHD and the need for long immunosuppressive treatments, new graft manipulation techniques, such as CD45RA or CD3αβ/CD19 depletion of lymphocytes, have been developed [6,7]. These techniques have successfully controlled GVHD, but they induce a delayed immune reconstitution that may increase life-threatening fungal or viral infections. Among these are HHV-6 infections, that can cause exanthema, kidney and liver failure, encephalitis, graft failure, or even the development of GVHD [12-15]. Therefore, it is important to recognize the variety of initial clinical manifestations that HHV-6 infection may produce, including fever, cutaneous rash, or mild neurological signs and start a diagnostic procedure immediately. Our case illustrates a highly aggressive HHV-6 infection that progressed to multi-organ failure and death after a fully matched unrelated donor myeloablative HSCT whose graft was manipulated with a CD34-positive selection followed by a CD45RA naïve T cell-depletion. This is consistent with a recently reported increased incidence of HHV-6 infections and the use of naïve T cell-depleted grafts of haploidentical stem cell transplantation in pediatric patients, although, in contrast with our case, the clinical evolution of these patients was not fatal [18,19]. Moreover, we describe an HHV-6 infection in an adult patient and after a different type of transplant, a matched unrelated donor HSCT.

Although there are some preliminary initiatives with the infusion of NK cells immediately posttransplant as a prophylaxis of viral infection [20], there is no generally accepted strategy in terms of detection, early monitoring, or prophylactic treatment for HHV-6 in patients undergoing allogeneic HSCT with or without manipulated grafts. However, pre-transplant and post-transplant serial PCR determinations could help to make an accurate diagnosis and, consequently, establish early treatment with ganciclovir or foscarnet. A previous negative HHV-6 PCR does not exclude the need for further PCR tests, especially when symptoms or signs consistent with HHV-6 reactivation appear. Due to the high number of viral copies detected and rapid clinical deterioration, ganciclovir and foscarnet were introduced simultaneously in this case. Despite an initial drop in viral copies, the patient developed a multi-organ failure and died of septic shock from *Enterococcus faecium*.

It is important to consider that HHV-6 can be integrated in germline, being these subjects strongly positive in PCR [21] and making diagnosis difficult. A previous negative HHV-6 PCR excluded this possibility in our patient. Another relevant aspect is the rarely described relationship between HHV-6 and the development of hemophagocytic lymphohistiocytosis, mainly in pediatric patients [22,23]. This HHV-6 related hemophagocytic lymphohistiocytosis may be a serious and potentially life-threatening complication [24].

This very severe case reflects that HHV-6 infection must be highly suspected not only in haploidentical HSCT but also in fully matched unrelated donor HSCT, especially when CD45RA T cell-depleted grafts are infused. The clinical evolution may be rapidly fatal even when combined treatment with ganciclovir and foscarnet is used. Therefore, it is important to make the diagnosis and start antiviral treatment as soon as possible, for which serial PCR determination is highly suggested whenever a clinical suspicion of HHV-6 infection appears.

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