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Neurological manifestation of CMV disease after allogeneic haematopoietic stem cells transplantation – a case report

Cytomegalovirus infection is one of the major causes of morbidity and mortality in patients after haematopoietic stem cells transplantation. Before engrafment of the transplanted cells the patient has no functional immune system. CMV remains latent in peripheral blood leukocytes and reactivates in seropositive patients as secondary infection. It can also manifest as a primary infection in patients who were seronegative before transplantation but receive stem cells from seropositive donor or acquire infection from exogenous sources, e.g. blood product. Active CMV infection can manifest as fever, fatigue, leucopenia, liver function disturbances or as hepatitis, colitis, myelitis, chorioretinitis, pneumonia with a high associated mortality rate (1). CMV infection occurs more commonly in allogeneic transplantation compared to autologous. Risk factors for disease include: recipient seropositivity, T-cell depletion, graft source unrelated donor, graft versus host disease, and failure of lymphoid reconstitution following HSCT (1, 5).

CASE REPORT

A 4-year-old girl diagnosed as having MDS, three months later underwent allo PBSCT from a HLA identical unrelated donor. At the time of transplantation the patient was CMV seropositive, the donor was CMV seronegative.

Pretransplant conditioning included busulfan 4 mg/kg daily for 4 days, cyclophosphamide 60 mg/kg daily for 2 days, melfalan 140 mg/m^2 once. Antithymocyte globuline and cyclosporin A with short-term methotrexate were administered for GvHD prophylaxis. Engrafment of leukocytes > 1.0 x 10^9 was noted on day +15 and of platelets > 20.0 x 10^9 and > 50.0 x 10^9 on day +23 and on day +26, respectively. Complete chimerism with PCR method was found on day +24. Acute GvHD grade II/III involving the skin and gastrointestinal tract developed on day +17 and oral prednisolone followed by MMF were administered. On day +20 the CNS malformation – Arnold-Chiari / Dandy-Walker type was found accidentally, when the CT scans of the head were performed because of symptoms of intracranial hypertension.

CMV reactivation was diagnosed on day +25 by detection of CMV antigenaemia in peripheral blood granulocytes. 16 of 450,000 cells containing viral protein CMV pp65 were found and pre-emptive treatment with gancyclovir and intravenous immune globuline was started. After 2 weeks of treatment CMV antigenaemia increased to 120 positive cells and foscarnet was substituted for gancyclovir. During 5 weeks of treatment slow extinction of CMV antigenaemia in peripheral blood was observed. At the time of resolving CMV antigenaemia severe low back and lower limbs pain with abasia and astasia occurred. Several symptoms of radiculitis were found with the neurological examination – progressive muscular weakness, hyporeflexia especially in lower limbs and positive

radicular signs. Within few next days ptosis of left upper eyelid and nystagmus occurred. Cytosis of 50 mononuclear cells per μl and cytomegalovirus by PCR were found in the cerebrospinal fluid. At the same time PCR test for CMV in the blood was negative. PCR test for detection of other viruses – HHV, EBV, HHV6, HHV7, HHV8 in the blood and CNS fluid were also negative. Spinal MRI scans showed thickening of the roots of cauda equina and the medullary cone confirming radiculitis (Fig. 1). Antiviral treatment was continued. Last follow-up was on day +103 after HSCT; about 4 weeks after neurological signs occurred. The girl is now in improving condition. Ptosis of the upper eyelid and nystagmus resolved almost completely, but we still observe muscular weakness with hyporeflexia and radicular signs. Dysbasia maintains, but the girl starts walking on all fours.

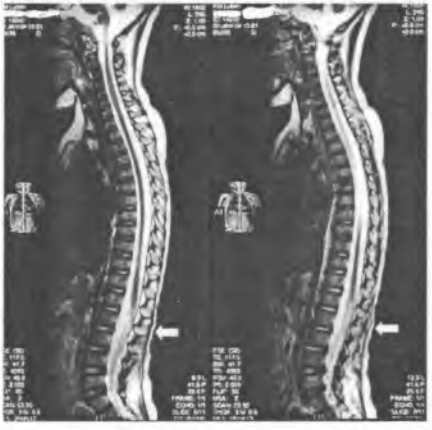

Fig. 1. MRI scans of the spinal cord showing thickening of the roots of cauda equina and the medullary cone confirming radiculitis

DISCUSSION

CMV infection is the most common viral infection after haematopoietic cells transplantation (1). Active CMV infection may be asymptomatic. Patients are classified as symptomatic if they have one or more of the clinical symptoms of pneumonia, enteritis, hepatitis, myelitis, together with detection of CMV in bronchoalveolar lavage, gut or liver biopsy or CNS fluid by culture, immunohistochemistry, *in situ* hybridization or PCR. Symptomatic CMV disease is related to a high mortality rate (3). Our patient developed symptoms of neuroinfection (radiculitis) with concomitant detection of CMV in CNS with PCR method. First CMV antigenaemia in the blood preceded diagnosis of CMV disease by about 5 weeks and CMV antigenemia in the peripheral blood almost completely resolved (2 positive cells for 500,000) when first neurological symptoms occurred. In the Gor et al. study first blood PCR-positive result preceded diagnosis of CMV disease by a median of 70 days, in the Matthes-Martin et al. study the median interval between the occurrence of viraemia and disease was 4, 5 weeks (1, 3).

The most important risk factor of CMV infection is pre-transplant serologic status of recipient and donor (R/D). As reported in many studies, recipient seropositivity had a significant impact on the incidence of CMV viraemia and disease. Seropositive recipients are at high risk for reactivation of the virus (1, 5, 6). It has been shown in the Gor et al. study that seronegative donor for CMV seropositive patient can increase the risk of CMV infection. They showed that seropositive recipients of a seronegative marrow had a higher median viral load than all other recipient-donor combinations (1). In the Matthes-Martin et al. study, CMV–PCR positive patients had a significantly reduced incidence of disease if the donor was seropositive and finally they concluded that in their study CMV-seronegative donor status was the only factor associated with a significantly increased incidence of disease (3).

Gratama et al. reported a higher incidence of CMV antigenaemia and disease after HSCT from CMV-seronegative donors (2). It could be explained by adoptive transfer of immunity from the donor resulting in reduced viral replication (1).

Stem cells transplantation from donors other than HLA-identical siblings increase the risk of CMV disease (5, 6). However, in the Gor et al. study no difference between the patients who received marrow from relatives or unrelated donors was observed (1).

It has been shown in many studies that occurrence of acute GVHD significantly increases the risk of CMV infection. Immune deficiency is associated with GVHD, e.g. activation of CMV-specific T-lymphocytes, essential for controlling CMV infection, is delayed in the presence of severe GVHD (1, 4, 6).

An interesting question remains whether the CNS malformations diagnosed in our patient have had any impact on the occurrence of neurological CMV disease? We were not able to find any data confirming such supposition. The child developed normally in the pretransplant period and no neurological abnormalities were observed at that time.

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SUMMARY

A 4-year-old girl who underwent allo HSCT from unrelated donor and developed neurological CMV disease in early postransplant period was described. She had clinical symptoms of radiculitis confirmed with spinal MRI scans with concomitant detection of CMV in CNS by PCR. Several risk factors for CMV disease in the presented case were discussed.

Neurologiczna manifestacja infekcji cytomegalowirusowej
po allogenicznym przeszczepieniu komórek hematopoetycznych – opis przypadku

Przedstawiamy przypadek 4-letniej dziewczynki, u której po allogenicznej transplantacji komórek hematopoetycznych od dawcy niespokrewnionego wystąpiła objawowa infekcja cytomegalowirusowa pod postacią zapalenia korzeni rdzeniowych. Omówiono czynniki ryzyka wystąpienia objawowej infekcji CMV w opisywanym przypadku.