Epstein-Barr Virus Infection after Stem Cell Transplantation: New Concepts Are Needed Both for the Donor and the Recipient

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(See the brief report by Teira et al. on pages 892–5)

Epstein-Barr virus (EBV) infection and reactivation is an increasingly common complication among patients with immunodeficiency, particularly patients who have recently undergone allogeneic hematopoietic stem cell transplantation (HSCT). Traditionally, reactivation of EBV infection after HSCT most often induces post-transplant lymphoproliferative disorders (PTLDs) [1]. However, in recent years, it has become clear that PTLDs are only the tip of the iceberg, with an increasing number of cases of EBV infection manifesting in patterns other than PTLD, including neurological disease, infectious mononucleosis, and viremia. After myeloablative cytoreductive therapy, as well as reduced-intensity conditioning regimens [2] and HSCT, a period of deep cellular immunodeficiency follows, until the donor-derived immune system has sufficiently regenerated. As a result of the lack of immunosurveillance, endogenous viruses, such as EBV, may be reactivated, or exogenous viruses may reinfect the patient and cause disease [3]. Specific T cell depletion of stem cell grafts and the use of antithymocyte globulin, which reduces the number of host-derived T cells without affecting the B cell lineage, contributes together to a state in which EBV-infected B cells can proliferate without any blocking activity of cytotoxic T cells from the recipient or from the donor.

Teira et al. [4] describe a new site of EBV infection after transplantation: the lungs. In their case, both the donor and the recipient were seronegative for EBV 1 month before transplantation, yet EBV infection originating from donor-derived bone marrow occurred. This raises many critical issues regarding the usual screening performed worldwide before transplantation. Do we now have to change the protocol and perform PCR analysis for EBV instead of detecting the presence of anti-EBV antibodies? Moreover, the pretransplantation evaluation was made 1 month before the transplantation. Do we now have to change the scheduling of this evaluation and perform it closer to the transplantation date? Furthermore, although the patient received a bone marrow–derived graft, the donor was checked for the presence of EBV only in the peripheral blood. Thus, it may appear that we should examine the exact site from which the donated graft is taken, thereby decreasing the probability of such cases.

The patient discussed in Teira et al. [4] had sickle cell anemia, which has a well-known association with pulmonary crises. This may point to the lungs as an area prone to develop problems after transplantation, such as infections or bronchiolitis obliterans (as a sign of pulmonary graft-versus-host disease). In addition, knowing that receipt of antithymocyte globulin is a risk factor for the development of EBV reactivation or reinfection after transplantation, it may be worthwhile to indicate those patients for whom the use of antithymocyte globulin should be avoided because of risk factors that the patients may have at baseline.

However, this case sheds light on more general issues associated with transplantation. The case described in Teira et al. [4] paves the way toward the augmentation of risk-based conditioning regimens administered before transplantation. EBV infection status should be included in the risk list for each patient before transplantation. Patients may not get specific conditioning medications if they have a specific risk factor in their background. On the other hand, patients who are at risk for the de-
development of EBV reactivation or reinfec-
tion after transplantation may benefit
from EBV-specific adoptive cellular ther-
apy as the result of receiving EBV-specific
T cells with the stem cell graft.

In their case, Teira et al. [4] describe the
treatment protocol that their patient re-
ceived, which included rituximab injec-
tions and corticosteroids. Cyclosporine
was discontinued because of renal toxicity
but not as part of the treatment.

Although the emergence of EBV infec-
tions after transplantation in patterns
other than PTLD has become more fre-
quent in recent years, the best way to treat
such cases is not yet well established. This
should prompt the medical microbiolo-
gists, as well as the stem cell transplantation
societies, to develop guidelines and
comprehensive protocols for the treat-
ment of EBV reactivation or reinfection
after transplantation. Such a protocol will
take into consideration the immune status
of the patient, the risk of developing graft-
versus-host disease, the patient’s EBV
load, and many other parameters that are
important for the management of this life-
threatening situation. In weighing the ben-
efits and costs of using rituximab after
HSCT, one should remember that anti-
CD20 antibodies do much harm in terms
of the repopulation of donor B cells, which
indirectly may affect immune reconstitu-
tion and the ability of the body to over-
come infections by pathogens other than
EBV. Thus, there will be cases in which
discontinuation of anti–graft-versus-host
disease immunosuppressant treatment,
such as cyclosporine, may be enough to
control the spread of the virus.

In summary, viral infections after trans-
plantation have increased in importance
in recent years. Describing new sites that
are prone to infection by specific patho-
gens, as well as appropriate treatment
methods, is expected to shed light on the
mechanisms underlying immunity in dif-
ferent physiological and pathological
states, leading to a better understanding
of such cases and to the design of inno-
vative potential future strategies and
medications.

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References

stein-Barr virus associated B cell lymphopro-
liferative disorders following bone marrow
incidence of EBV-related disease following pae-
diatric stem cell transplantation with reduced-
Epstein-Barr virus infection after allogeneic
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Epstein-Barr virus infection with pneumonia
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(in this issue).