Title: Graft versus EBV-related posttransplantation lymphoproliferative disease

Authors:

Gerhard Behre (gerhard.behre@medizin.uni-halle.de)
Thomas Weber (thomas.weber@medizin.uni-halle.de)
Sebastian Theurich (sebastian.theurich@medizin.uni-halle.de)
Maximilian Christopeit (maximilian.christopeit@medizin.uni-halle.de)

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Author's response to reviews: see over
Dear Professor Kidd,

we are grateful to have our manuscript entitled “Graft versus EBV-related posttransplantation lymphoproliferative disease: a case report” reviewed by experts from the field and have implemented their very helpful comments and criticism into our manuscript which we resubmit in a revised form along with this letter.

We addressed the points in detail,

Reviewer Eeva Juvonen:

Was EBV excluded from the samples showing relapse and transformation?

EBV was excluded by a negative LMP1 stain. This has been amended in the text.

Would it be possible that transformation in fact was lymphoproliferation caused by EBV-reactivation?

This is possible and an excellent differential diagnosis but has to remain, on the basis of the data we present, highly speculative. We
have included into the text the notion that the relevance of the PCR positivity is not clear.

It would be nice to get more accurate timing of the development of the nodules and progressive erythema in regard to the transplantation as well as the survival data of the patient.

This has been amended into the manuscript.

What do the authors mean by graft versus (altered) host reaction? Was PTLD the altered host?? If so, why not simply use graft versus PTLD?

We have removed any speculations about graft versus PTLD as the diagnosis PTLD is not established for the patient reported, and regard the phenomenon we observe a graft versus lymphoma effect.

Are the authors claiming that massive diarrhea was a manifestation of EBV infection /reactivation?

We do not claim that this was the case as we do not have any data about such speculations. The differential for our patient’s diarrhea again includes many disease, the most likely being alloreactivity / graft versus host disease.

Reviewer 2 Tamilarasu Kadhiravan

1. It is unclear from the description, what was the timing of the appearance of the erythema – presumably, it was after the infusion of stem cells.

The erythema occurred after the patient had engrafted. This has been made clear in the text.

2. The basis for a diagnosis of post-transplant lymphoproliferative disorder (PTLD) in this patient is unclear. The authors state, the cutaneous nodules appeared during conditioning (before the transplant). Is it not likely that these
nodules were a manifestation of her progressive lymphoplasmacytic lymphoma?

3. The diagnosis of PTLD is straightforward in recipients of solid organs and in recipients of haematopoietic cell transplants for indications other than a lymphoma. But, in a patient whose primary disease was a lymphoma, the diagnosis of PTLD is challenging. In fact, PCR-positivity for EBV may not be diagnostic of an EBV-related PTLD in this particular setting. It might well have been an EBV-related lymphoma to begin with. Did the authors consider this possibility?

4. Most of the EBV-related PTLDs in recipients of haematopoietic cell transplants are of donor cell origin (i.e., the EBV-infected B-cells arise from the donor). This being the case, a graft (donor) versus PTLD (again donor in origin) reaction seems conceptually incompatible. Do the authors have any hypothesis to explain this anomaly?

We agree with the reviewer and have restricted all speculation about the PTLD nature of the lymphoma to the discussion section.

Again, we thank you and the reviewers for a critical reading of our manuscript and hope that you accept our revised version for publication.

Kind regards,

Yours sincerely

Gerhard Behre