

KSHV reactivation in post-transplant Kaposi sarcoma

To the editor:

In their article on post-transplant Kaposi sarcoma, Barozzi *et al.*¹ elegantly show that in five of the eight Kaposi sarcoma patients investigated, tumor cells infected with Kaposi sarcoma-associated herpesvirus (KSHV) display phenotypic and genotypic features of donor origin. Based on these findings, the authors advocate the use of donor-derived, KSHV-specific T cells for the treatment of post-transplant Kaposi sarcoma.

The medical relevance and clinical implications of these findings need to be evaluated in the appropriate context, however. In particular, the seroepidemiological framework underlying the occurrence of post-transplant Kaposi sarcoma in different geographic areas must be considered.

We have previously shown that in northern Italy, where the seroprevalence of KSHV among organ donors and recipients is 4% and 6% respectively (C.P. *et al.*, unpublished data), post-transplant Kaposi sarcoma has an incidence of 0.9%, and 90% of those cases occur in patients who were seropositive at the time of transplantation². Our data are in agreement with other retrospective studies^{3,4}. We can thus infer that KSHV reactivation is the most important pathogenetic event (>80% incidence) underlying postrenal transplant Kaposi sarcoma in the western world.

In this regard, it is noteworthy that in the only Kaposi sarcoma patient studied by Barozzi *et al.* with unequivocal serologic evidence of reactivation, the findings argue against a donor origin of Kaposi sarcoma tumor cells. We therefore advise that baseline serologic testing for KSHV be performed in all transplant donors and recipients to distinguish between viral transmission and reactivation in case of Kaposi sarcoma development. This should allow rational use of investigational immunotherapeutic strategies based on donor-derived, as

opposed to recipient-derived, KSHV-specific T cells.

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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Luppi *et al.* reply:

We would like to thank Parravicini *et al.* for their interest in our work. In their correspondence, they argue that the majority of transplant Kaposi sarcoma cases are due to reactivation of a pre-existing infection with KSHV, rather than caused by transmission of the virus or virus-infected cells from the organ donor to the recipient, as described in our paper. Parravicini *et al.* stress that in the case of a reactivated viral infection, our suggestion to use KSHV-specific T cells for adoptive therapy would obviously have to be based on recipient-derived, rather than donor-derived, T cells.

We agree entirely with Parravicini *et al.* that the majority of transplant Kaposi sarcoma cases may be the consequence of a reactivated viral infection. This was, however, not the point of our paper, which described transmission of a KSHV-infected cell from donor to recipient that could subsequently lead to the development of a Kaposi sarcoma lesion. As for the frequency of donor-derived versus recipient-derived KSHV in the pathogenesis of transplant Kaposi sarcoma, we have recently reviewed the published literature on this issue⁵. It appears that of 50 well-documented and published cases of

transplant Kaposi sarcoma, 16 (32%) could have been caused by donor-derived virus. Therefore, donor-derived virus may be responsible for the development of transplant Kaposi sarcoma more frequently than suggested by Parravicini *et al.*, and this figure may depend on local prevalence of KSHV. Serologic testing for KSHV before and after transplantation may indeed be helpful, as mentioned by Parravicini *et al.* In addition, in order to substantiate the origin of KSHV in a transplant patient with Kaposi sarcoma, peripheral blood DNA from the donor should be stored at the time of transplantation. This would allow the comparison of KSHV strains in the donor and the recipient by sequencing of the hypervariable *K1* gene or by restriction fragment-length polymorphism analysis^{6,7}.

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