Author's response to reviews

Title: Late pulmonary metastases of renal cell carcinoma immediately after post-transplantation immunosuppressive treatment: a case report.

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Author's response to reviews: see over
Thank you for reviewing our manuscript. We would like to answer the questions and address the reviewers’ comments. We hope that the new version of our manuscript will be accepted for publication in your journal.

Reviewer 1, Richard Borrows

1. At initial presentation in 1986 there was no evidence of a renal mass according to sonography. At that time the patient had only renal insufficiency. The renal mass was detected in 1992 after sonographical examination and was later confirmed by CT scan. The diameter of the lesion was 5 by 6 cm. In our case transplantation was done 8 years after the initial detection of the tumor.
2. The scan performed in 1992 was a surveillance annual scan without clinical symptoms suggestive of malignancy.
3. We have added to the text a description of tumor stage abbreviation pT2pN0M0 as tumor localized in kidney parenchyma without metastases into regional lymph nodes and elsewhere.
4. We added the description of immunosuppressive treatment administered to the patient according to the standard protocol accepted in our hospital. The regimen included: Prednisolone, Tacrolimus and Mycophenolate. The immunosuppression was not augmented during since there were no signs of rejection.
5. We think that fig.1 is beneficial for the manuscript.
6. More detailed explanation of the microsatellite analysis with corresponding references are added to the Fig.2 legend.
7. The current knowledge about cancer immune surveillance, tumor immune escape and tumor dormancy suggest that this is not just a coincidence. Late recurrence without immunosuppressant could be also associated with some unobserved changes in the immune status of patients, but we do not have any documented evidence supporting it. Thus, it is important to describe cases when recurrence happens soon after immunosuppression.
8. Suggestion to revise existing guidelines of 2 to 5 years period prior to transplantation, to inform patients that immunosuppressive medication increases risk of cancer recurrence soon after the transplantation, important to have more frequent check ups.
9. This assay is commonly used for linkage mapping studies, association studies, and identification of organisms (Becker, 1997). It has been reported to be useful for assessment of chimerism in graft-versus-host disease (Hochberg, 2003), for identification of the site of origin of unknown primary tumor (Califano, 1999), and for determination of donor-recipient origin in posttransplant lymphoproliferative disorders (Larson, 1996).
10. The mistake has been corrected.
1. Introduction: More references added regarding RCC recurrence, pulmonary metastatic recurrence, and higher metastatic lapses alter transplantation. However, we could not find specifically publications demonstrating RCC soon after transplantation.

2. Case Presentation: Details of the immunosuppressive regime added

3. Discussion: relative increased risk of recurrence in early posttransplant phase discussed. Discussion has been modified.

4. There is no mistake; indeed, tumor cells arising in presence of a fully functional immune system are less immunogenic than those developing in immunosuppressed individuals. This statement does make sense according to the current knowledge about the anti-tumor role of the immune system, including cancer immunosurveillance and generation of tumor immune escape variants under selective pressure of competent immune system. We are sorry that we did not explain this topic well. We have added new references and more detailed description of the tumor immune selection mechanism.

5. This sentence has been eliminated.

6. Various factors have been identified as possible contributors to tumor dormancy and subsequent recurrence, including tumor angiogenesis, cell proliferation and cell cycle arrest, cancer cell interactions with the microenvironment, and changes in the immune status [23, 24]. Various published results have described that oncogene inactivation can induce tumor regression and that oncogene reactivation leads to rapid tumor formation MYC oncogen inactivation under certain circumstances can induce a state of tumor dormancy [25]. There are reports demonstrating that at least in some cases tumor dormancy can be interrupted by a transient change in the microenvironment due to local inflammation [26]. Animal studies also indicate importance of T-cell immunity in the induction and maintenance of tumor dormancy [27].

7. “Most likely” changed to “we propose”.

Sincerely,

Dr. Francisco Ruiz-Cabello
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