Author's response to reviews

Title: HIV-Associated Bladder Cancer: A Case Series Evaluating Difficulties in Diagnosis and Management

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Version: 2 Date: 26 July 2009

Author's response to reviews: see over
Dear Editor,

Thank you for the favorable review of our manuscript. We have revised our paper to answer all of the comments received from reviewers. The following is a summary of how we addressed the reviewer’s comments in our manuscript HIV-Associated Bladder Cancer: A Case Series Evaluating Difficulties in Diagnosis and Management.

**Reviewer #1**

*I believe the statement that “Bladder cancer should be added to the growing list of Non-AIDS defining cancers likely encountered in HIV-infected patients” is misleading in the sense that the statement implies a higher incidence rate in the HIV population compared to non-HIV infected patients. All else being equal (as determined by the authors), we should evaluate the HIV patient similar to any other patient with signs and symptoms suggestive of an urothelial neoplasm.*

We agree with the reviewers’ comment and have adjusted the text accordingly.

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We expanded our discussion on this point. We have now included that there is a theoretical increased risk of disseminated infection in HIV-infected patients receiving intravesical BCG, however, only a single case report of this complication exists in the literature. Intravesical BCG has been used safely in this population. Moreover, BCG exerts its anti-tumor effects via recruiting CD4+ helper T cells, which are reduced in HIV-infected patients. Given the combination of suboptimal tumor control with the risk of possible disseminated infection, we recommend caution or avoidance of this agent. If its use is considered, we would recommend evaluation of the CD4+ count prior to treatment.

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*The authors need to clarify what is meant by the term urethral-ileal neostomy. Do they mean “orthotopic neobladder creation”?*

Yes, this change was made in the manuscript.

**Reviewer #2**

*When we always try to evaluate the patients with gross hematuria or microscopic hematuria, we should rule out bladder cancer. This is not especially HIV patients.*

We agree with the reviewer that all patients with hematuria or microscopic hematuria should be evaluated. As we discuss in the manuscript, there is a broad range of possible etiologies for hematuria...
in the HIV-infected population and the consideration of bladder cancer can be delayed or, possibly, overlooked completely.

You wrote CD4 value, but “How are CD8 value? Or CD4/CD8 ratio?” I think that it is necessary to write CD4/CD8 for immunodeficiency patients.

While CD4/CD8 ratios are often obtained in HIV-infected patients, by convention, only the absolute CD4 cell count is reported as a measure of HIV-related immunosuppression. Well accepted HIV/AIDS classification systems, including the CDC and WHO, use only the CD4 cell count. Therefore we have reported only the CD4 cell count in this paper.

Reviewer #3

As already showed, bladder cancer is one of the NDACs. This is the reason there are few case reports. Not because limited number of patients who have both. Nowadays, most of all urologists have experienced to see HIV infected patients. They were educated already how to deal with this disease before graduating their medical schools. This report cannot provide more information nor any impact to general urologists.

We acknowledge the inherent limitations of this small observational study, but we are pleased to present the largest series on bladder cancer in HIV-infected patients to date. There are considerations for diagnosis and management in this population, which are not the same as the general population. We think it is important to know the behavior of this cancer in the setting of immunosuppression.

Thank you for the opportunity to revise our submission to your journal. We appreciate the time and effort of your reviewers and agree that the changes suggested make our manuscript much stronger. Please feel free to contact us for further information or clarification.

Sincerely,

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