

RESPONSE TO REVIEWERS

Oct 23, 2016

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 29475_revised manuscript)

Title: Hepatic Kaposi Sarcoma: A Case Report and Review of the Literature

Running title: Hepatic Kaposi Sarcoma

Authors: Brett Daniel Van-Leer Greenberg , Abhisake Kole , Saurabh Chawla

Name of Journal: *World Journal of Hepatology*

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Manuscript Type: Minireviews

The manuscript has been improved according to the suggestions of reviewers:

1. Revision has been made according to the suggestions of the reviewers.
Please see the following page for reviewers' comments and our revisions and response.

Thank you again for publishing our manuscript in the World Journal of Hepatology

Sincerely yours,

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REVIEWER 1:

The review article is well organized and properly processed on the basis of a case.

RESPONSE:

We appreciate your favorable review of our manuscript. We hope that this manuscript would be useful for other readers as well.

REVIEWER 2:

1. 1. Rather extensive copy editing is necessary.

RESPONSE: We thank the reviewer for their review and comments. Based on your suggestions we have extensively copy edited the manuscript in all sections.

2. Please refer to the Staging system of Kaposi sarcoma related to HIV infection:
<http://www.cancer.org/acs/groups/cid/documents/webcontent/003106-pdf.pdf>

RESPONSE: We thank the reviewer for highlighting the importance of the staging system and providing an appropriate reference. We have incorporated the staging system into our revised manuscript as below:

As KS is a disseminated angioproliferative virally mediated malignancy, classic tumor, node, metastasis (TNM) staging as used in other cancers does not accurately prognosticate disease or dictate treatment. AIDS Clinical Trials Group (ACTG) Oncology Committee has codified staging of AIDS-associated KS [i]. The ACTG staging system risk stratifies patients low risk (0) or high risk (1) based on three criteria: Tumor burden (T), poor risk (T1) is defined by presence of extensive cutaneous, oral disease or visceral disease. Immune status, poor risk (I1) is defined by CD4 count of less than 150 cells/ μ L. For systemic illness, poor risk (S1) is defined by the presence of constitutional symptoms poor performance status or other opportunistic infections. While these criteria were validated in the pre-ART era, post-ART therapy, a CD4 cutoff of 100 cells/mm³ has an unclear role in predicting mortality [ii, iii].

3. Stage is an important determining factor. What was the stage of the presented case?

RESPONSE: We agree with the reviewer and thank them for highlighting this inadequacy in our manuscript. We have revised the manuscript to reflect the staging in our patient as below:

The diagnosis was most consistent with acute liver injury secondary to infiltrative hepatic Kaposi Sarcoma, stage T1,I1,S1.

4. Please elaborate on the incidence of isolated KS in the liver (in the absence of GIT or cutaneous involvement) in HIV +ve cases as well as in HIV –ve cases.

RESPONSE: We appreciate the reviewer's comments. It is challenging to define the incidence of isolated KS in the liver as most cases are asymptomatic and thus not documented. Most of the prevalence estimates are from post-mortem series. Also, isolated hepatic KS in the non HIV setting has not been well reported. We, however agree with the reviewer in that this should be reported as best possible and have amended our manuscript as below:

The most common presentation of KS is a cutaneous papular disease with lesions on the lower extremities, nose, oral mucosa, and genitalia.

Hepatic KS is typically asymptomatic and rarely diagnosed in life. **Therefore the true incidence of Hepatic KS is not well-documented and is limited to small case series and reports.** Prevalence of hepatic KS has primarily been determined from autopsy series with small sample sizes, which accounts for the wide variation in prevalence reported. In one autopsy series, approximately 34% of AIDS-related KS cases involved the liver while in another report, 8.3% had liver involvement^[iv,v]. In another retrospective review, hepatic involvement was present in 9 of 41 patients or 22% of cases of AIDS-related KS in post mortem dissection^[vi]. **In this study ante-mortem liver involvement was suspected in only one patient, in which a CT scan demonstrated hepatosplenomegaly with a confluence of hypodense lesions in the left hepatic lobe. This patient expired 15 days later an autopsy showed disseminated KS.** Schneiderman et al.^[vii] found KS on liver biopsy in 18.6% of AIDS patients making KS the most common postmortem intrahepatic AIDS-specific lesion. All of these patients already had a diagnosis of extrahepatic KS at time of biopsy. In contrast, 21 of 32 (65.6%) autopsies with extra-hepatic KS did not demonstrate this lesion in the liver^[viii].

As mentioned above, most cases of hepatic KS were not clinically significant. In the study by Schneiderman et al, there were no statistically significant differences in aspartate transaminase, alanine transaminase, lactic dehydrogenase, alkaline phosphatase and bilirubin values among patients with (n=9) and without (n=32) liver involvement by KS. However, in the few reported patients with clinically significant disease, a rapid progression to liver and multi-organ failure has been reported, usually with fatal outcomes (Table 1). **In the non- HIV population, the incidence of post-liver-transplant KS is reported to be 0.2% in the United States and is more prevalent in patients of Mediterranean, African,**

and Arabic descent^{ix}. KS affected 4.7% of renal transplant patients in Saudi Arabia, 2.4% of 330 recipients in Israel and 0.52% of 7923 recipients in France. While there is a well described clinical burden of post-transplant lymphoproliferative disorder (PTLD) including cutaneous and visceral manifestations of KS, there is no described literature of post-transplant hepatic KS.

5. The pathological photos need to be of a higher quality. Also the legends to the figures need to be standardized and in greater detail with arrows to show the intended lesion.

RESPONSE: We thank the reviewer for highlighting this inadequacy in our manuscript. We have modified the figures, legends and added arrows to show the intended lesions.

6. Are the authors implying that fatty change in the liver is an integral histologic feature of Kaposi sarcoma in the liver. Fatty change is an incidental finding and has not been related to HIV or HHV 8 infection. So referring to the fatty change in the liver in US diagnosis as an integral part is not accepted.

RESPONSE: We thank the reviewer for this important comment. We agree that fatty change is NOT an integral feature of KS in the liver and have edited our manuscript to clarify the histological and radiological imaging characteristics of KS as below:

Hepatic Kaposi Sarcoma has characteristic findings on individual imaging modalities that can help delineate clinically significant disease. Abdominal ultrasound imaging of the liver can demonstrate inhomogeneous cystic lesions with multiple hyperechoic periportal bands and nodules or hyperechoic nodules along the peripheral branches of portal veins. Computed tomography is characteristic for inhomogeneous hepatomegaly with numerous small hypodense liver nodules, often in the periportal area with portal and delayed hilar contrast enhancement ^[x] (Figures 4). Mild hepatomegaly is a non-specific finding in 19% of patients with AIDS-related KS^[xi]. MRI shows nodules that are hyperintense on T1-weighted in-phase images and hypointense on T1-weighted out-of-phase images owing to the presence of fat (Figure 5). T2-weighted images do not show signal changes, and in the late hepatobiliary volumetric interpolated breath hold examination (VIBE) there is no specific uptake of contrast ^[xii,xiii].

Image guided biopsy of hepatic nodules in patients suspected to have liver involvement demonstrate spindle cells with hyaline globules with large, irregular nuclei, associated with slit-like vascular spaces and hemosiderin accumulation, macrovacuolar steatosis,

large fibrotic portal spaces, bile duct ectasia and neoductogenesis. Staining on the perinodular tissues is positive for CD31, CD34, and factor VIII as can be seen in extrahepatic KS as well^[xiv].

7. Please refer to specific survival rates when discussing the prognosis of the different types with and without treatment.

RESPONSE: We thank the reviewer for highlighting the importance of discussing prognosis with and without treatment and have included that in our revision. See below:

Radiotherapy is a well established treatment and often produces highly effective therapeutic results with classic nodular KS but tends to be a palliative approach. While it may be a good modality for superficial lesions, electron beam radiation therapy (EBRT) has limited penetration beyond the dermis; deeper or unresponsive KS may be treated with standard non-EBRT approaches^{xv}.

Retinoid products appear to have an inhibitory effect on IL-6, a cytokine implicated in KS pathogenesis, and an antiproliferative effect on KS lesions^{xvi}. Application of alitretinoin gel, the only self-administered FDA-approved topical agent for cutaneous AIDS-KS, has shown efficacy for skin lesions of both classic and HIV-KS but has no role in systemic disease^{xvii}.

Studies comparing HAART plus chemotherapy to HAART alone showed the following: one trial comparing HAART plus doxorubicin, bleomycin and vincristine (ABV) to HAART alone showed a significant reduction in disease progression in the HAART plus ABV group (RR 0.10; 95% CI 0.01 to 0.75, 100 participants); there was no statistically significant reduction in mortality and no difference in adverse events. A total of five out of 65 T1 participants in the HAART plus liposomal anthracycline group died at the end of 12 months compared to four out of 64 participants in the HAART alone group (RR 1.23; 95% CI 0.35 to 4.38)^{xviii}.

Current first-line systemic therapy for advanced, progressive AIDS-KS are liposomal anthracyclines, including Pegylated liposomal doxorubicin (PLD). In a randomized control trial (RCT), PLD demonstrated superiority to previous conventional chemotherapy, bleomycin and vincristine (BV) with 58.7% vs. 23.3% (P<0.001) response rate and a decreased adverse event rate (10.7% vs 26.7%)^[xix]. Another RCT of liposomal daunorubicin verses doxorubicin, bleomycin and vincristine (ABV) showed no statistical difference in response rate or disease progression (25% vs 28%)^[xx]. Median survival time

was 369 days for participants in the liposomal daunorubicin group and 342 days for participants in the ABV group. When the analysis was restricted to patients receiving prior zidovudine, survival was improved in the liposomal daunorubicin group as compared to the ABV group ($p=0.26$; individual level data not provided). An additional non-randomised study showed a non-statistically significant overall mortality benefit from liposomal doxorubicin as compared to conservative management consisting of either bleomycin plus vinblastine, vincristine or single-agent antiretroviral therapy alone (RR 0.93; 95% CI 0.75 to 1.15, 29 participants)^{xxi}.

Interferon-alpha (IFN), has an array of antiviral and antiangiogenic properties, with dose-dependent efficacy in treatment of AIDS-KS^{xxii}. However, hepatotoxicity is a known side effect of IFN therapy and is therefore not recommended in the treatment of AIDS related KS.

Paclitaxel has systemic response rates from 59-71% and is approved as second-line treatment for KS^{xxiii,xxiv}. In randomized controls, paclitaxel does not demonstrate benefit over PLD in complete or partial remission and no mortality data were available according to Kaposi sarcoma staging^{xxv}. Less well tolerated than doxorubicin, adverse events include peripheral neuropathies, cytopenias, and gastrointestinal upset. Third line agents for AIDS related visceral KS include etoposide, bleomycin, vinblastine, and vincristine with overall response rates ranging from 23% to 36%. The median survival times are 11 (6 to 20) months in the bleomycin only group and 13 (7 to 36) months in the ABV group. With extensive side effect profiles, including secondary malignancies, these treatment modalities are maintained in resource-limited settings^{xxvi,xxvii}.

Although HAART with or without chemotherapy is the current recommended treatment, novel targets are being explored including inhibitors of angiogenesis and matrix metalloproteinases. These drugs are currently in various phases of clinical trials^{xxviii}. Inhibition of HHV-8 replication with agents such as foscarnet and ganciclovir have also been explored^{xxix}.

Finally, it bears mentioning that treatment for HIV/AIDS in patients co-infected with HHV-8 can cause a paradoxical worsening of disease. In the Kaposi sarcoma AIDS AntiRetroviral Therapy (KAART) Trial, 23/112 (21%) of co-infected patients receiving ARV therapy developed Kaposi sarcoma-associated immune reconstitution inflammatory syndrome (KS-

IRIS), which was defined as a rapid worsening of KS beyond its natural course within 12 weeks of initiating ARV therapy. Of those 23 patients, 10 died, 9 of which had visceral KS. 18 patients in the study overall (16%) had worsening elevation in their liver enzymes and two patients (1.8%) died of liver failure. In this study, exclusion criteria included HIV-KS patients with direct serum bilirubin >85 µmol/L or aspartate aminotransferase or alanine aminotransferase >2.5 times the normal range^[xxx].

Biologic and targeted molecular therapies have demonstrated a supplementary or alternative role in AIDS-KS. In the AIDS Malignancy Consortium, a phase II trial of Imatinib looked at thirty patients, of whom ten patients (33.3%) achieved partial response, six (20%) had stable disease, and seven (23.3%) exhibited KS progression. Nine patients completed 52 weeks of imatinib therapy^{xxxii}. Bevacizumab, the humanized, antivascular, endothelial growth-factor monoclonal antibody, had a response rate in 5 of 16 patients who did not improve after the institution of cART and chemotherapy^{xxxiii}. Interleukin-12 had a response rate of 71% (95% confidence interval, 48%–89%) among 24 evaluable patients in a phase I and phase II trial. however, patients were ineligible if they had an aspartate transaminase level of more than 2.5 times the upper limit of normal or history of hepatic disease^{xxxiii}. Ongoing studies including a phase II trial for the utility of combined PLD and bevacizumab in the treatment of advanced AIDS-KS^{xxxiv}. Additionally, a phase I study for dosing and side effect profile of combination therapy with ipilimumab, an cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody and Nivolumab, specific for human programmed cell death 1 (PD-1) antibody treatment in advanced Kaposi sarcoma solid tumors.^{xxxv} These trials show that biologic and molecular therapies may have a role in the future as alternative treatment therapy for some patients with AIDS-KS.

8. Others forms of treatment have to be referred to in the section on treatment of KS.

RESPONSE: We thank the reviewer for this valuable comment. We have edited the manuscript and added other treatment options (please see highlighted section in Response to comment #7).

9. Many of the written sections need proper references.

RESPONSE: We thank the reviewer for their comments and have added references throughout the manuscript and as suggested by the reviewer.

REVIEWER 3:

The authors reported a case of hepatic kaposi sarcoma and reviewed the relevant literature. The case of nicely presented and the review was informative. This article is helpful for hepatologists in diagnosis and treatment of this disease in patients with high risks.

RESPONSE: We thank the reviewer for their review and kind comments. We sincerely hope that the article would be helpful and informative for the readers.

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