March 7, 2020

Dr. Hiten RH Patel
Editor-in-Chief, *World Journal of Clinical Oncology*

Dear Dr. Patel:

We are pleased to submit our revised manuscript entitled "Concurrent Renal Cell Carcinoma and Hematologic Malignancies: Case Series of 9 Patients". Point-by-point responses to the reviewer's comments are below.

We would like to thank you and the reviewer for your meticulous work and valuable advice. We hope that our manuscript will now be accepted for publication in *World Journal of Clinical Oncology*.

Reviewer #1, Comment #1: "Abstract. Page 2, Paragraph 2, Says; CASE SUMMARIES: Four patients were diagnosed; …a) It is possible, use percent of these cases. b) Please review the paragraph because this part is confuse. Page 2, Paragraph 3, Says; CONCLUSION: Long-term medical surveillance is;… a) In this part of the conclusion, I recommend to author focus propertly in the characteristics of these patients, and explain better immune system dysregulation because this is not explained in the abstract."

Response to Reviewer #1, Comment #3: We have added the percentage of patients in the "Case Summaries" section of the Abstract and have revised the "Case Summaries" paragraph to make it more clear, as follows: "Four (44%) patients were diagnosed with RCC prior to the HM, the diagnosis was simultaneous in 4 (44%) patients, and 1 (11%) patient was diagnosed with the HM prior to the RCC. No patients were treated with cytotoxic chemotherapy or radiation between the diagnosis of RCC and HM. Several unique features were seen in our case series, such as 3 simultaneous cancers in 1 (11%) patient, a splenectomy leading to remission of diffuse large B cell lymphoma without the use of chemotherapy in 1 (11%) patient, chemotherapy and rituximab for lymphoma resulting in a complete response in primary RCC in 1 (11%) patient, and immunotherapy providing an excellent response for primary renal leiomyosarcoma in 1 (11%) patient."

In the "Conclusion" section of the Abstract, we have added a statement about the characteristics of these patients and have provided more details about immune system dysregulation, as follows: "These findings highlight the potential role of immune system dysregulation in patients with the diagnosis of RCC and HM whereby the first malignancy predisposes to the second through an immunomodulatory effect. HM have the potential of being confused with lymph node metastasis from kidney cancer. Lymph node biopsy may be necessary at the time of initial diagnosis or in cases of mixed response to therapy. Long-term medical surveillance is warranted when a patient is diagnosed with RCC or HM. Clinicians should be aware of the higher prevalence of male gender and lymphoid malignancy with concurrent RCC and HM and that either of these conditions may be diagnosed first or they may be diagnosed simultaneously."

Reviewer #1, Comment #2: "Introduction. The introduction is interesting when they explain the characteristic of RCC and HM, and the most frecuent malignancy presented together whit RCC. They explain the immunedysregulation as a principal factor in the RCC and HM. However, they need to explain more the frecuency and incidence of these tumors and explain better the immunodysregulation and what type of immunomodulatory effect is present in this type of tumors."

Response to Reviewer #1, Comment #2: In the Introduction, we have provided more details about the frequency and incidence of RCC and HM occurring concurrently, as follows: "RCC is observed in the general population in 12.5 persons per 100,000 and HM in 31.8 per 100,000 [1]. The incidence of RCC and HM occurring in same patient is greater than that expected in the general population [1,2]. A higher than expected incidence of RCC concurrent with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) has also been reported [2-5]. Epidemiological studies have shown that the observed-to-expected ratio for occurrence of RCC in NHL patients were 1.86 to 2.67 [2,3]. Furthermore, it has been reported that patients with the diagnosis of NHL have an increased incidence of RCC, bladder carcinoma, lung carcinoma, brain tumors, and melanoma as well as other HM such as acute myeloid leukemia and Hodgkin's lymphoma (HL) [6,7]." In addition, we described the immunomodulatory effect in further details, as follows: "In this respect, immune dysregulation generates the lymphoma which subsequently leads to the development of solid tumors such as RCC. The surveillance for malignancy and immune dysregulation resulting from immune checkpoint inhibitors in these cases are only theories, and the exact mechanisms are unknown."

Reviewer #1, Comment #3: "Material and Methods: Comments: I suggest in this part delete this paragraph because is similar to the abstract and they don't explain propiertly material and methods, I suggest use case report o report cases and explain each case and the end of the text use table."

Response to Reviewer #1, Comment #3: We have removed the "Materials and Methods" section according to the Reviewer's recommendation. We have explained each of the cases completely and used Table 1 at the end of the text to highlight unique features of each case.

Reviewer #1, Comment #4: "Results: Case#2: Comments: The case 2 is interesting but I have a question about this case, The metastasic node where of RCC or LND? I don't understand if the patient die by kidney injury why they made a mention about radical nephrectomy, please explain this part. Case #9: Comments: These cases that the authors present are interesting, however, the descriptions are incomplete. In some description of cases the authors focus only in the treatment of the lymphoma, but they do not describe what happened with the kidney diseases. Is it possible that the authors complete the cases? if not, I suggest explaining in material and methods that the description of some cases is not complete due missing data regarding the follow up."

Response to Reviewer #1, Comment #4: We have added clarification to Case #2, as follows: "Immunohistochemistry confirmed the mantle cell lymphoma in the retroperitoneal lymph node." The patient underwent a radical nephrectomy and died of kidney injury 54 months later.

The descriptions of all of the cases presented in our case series are complete. We have specifically detailed the management and outcomes of both the RCCs and HMs in all of the cases.

Reviewer #1, Comment #5: "Figure 1. All the Photographies of figure 1 belong only one case? Please describe in the photography each case or it is possible use more radiographic imagen of the cases. It's possible that the author provide microscopic images of the cases, will be possible that the authors provide the histopathologic studies."

Response to Reviewer #1, Comment #5: All of the images of Figure 1 refer to Case #1. This case was especially unique to present CT imaging findings since the papillary renal cell carcinoma resolved after treating the follicular lymphoma with 6 cycles of bendamustine/rituximab. Histopathologic imaging was not available for this case.

Reviewer #1, Comment #6: "**Explain better immune system dysregulation What is the reason about the remission of the HM but minor remission of RCC, if it possible explain why some patients have overall survival without treatment that patients whit treatment."**

Response to Reviewer #1, Comment #6: We have addressed the reviewer's request in further detail and have added the following paragraph to the Discussion (Page 10): "We propose that immune dysregulation may be a potential explanation for both RCC and HM occurring in one host, however, this is solely a theory and the exact mechanisms are not known. It may be partly explained by the fact that both RCC and HM are well-known to respond to immunotherapy although they may have different clinical aggressiveness based on histology and grade. Both malignancies may be monitored without treatment at times based on histology, grade, and clinical behavior. Indolent disease may start to progress quickly due to transformation of the tumor to a more agrressive type. It appears in some cases that the host's immune system may partially control the tumor growth resulting in "stable disease" without a need for treatment. In such cases, intrinsic or extrinsic immunosuppression may lead to tumor progression."

Reviewer #1, Comment #7: "Table1. I think this is repetitive with the described cases and the results, thus, I recommend making a table with cases reported in other studies and then compare them with the authors' cases."

Response to Reviewer #1, Comment #7: The reviewer suggested in Comment #3 that we should explain each of the cases and then use a table at the end of the text. We have followed the Reviewer's Comment #3 and have explained each of the cases and used our Table 1 at the end of the text to highlight unique features of each case. We think it is important and similar to other articles in the literature to keep our pre-existing Table 1. We do agree that a new table with cases of concurrent RCC and HM in the literature would be beneficial. Per the Reviewer's suggestion, we have added a new table (Table 2) with cases reported in other studies and compared them with our cases in the Discussion, as follows: "The phenomenon of concurrent RCC and HM has been reported in the literature, with a focus on gender, timing of the diagnosis of RCC and HM, and most common HM (Table 2) [1-5,8,10,11]. All except one of the studies in Table 2 documented a higher number of men with both conditions. Interestingly, in Tihan's and Filippa's study of 15 patients with coexisting RCC and malignant lymphoma, 11 (73%) of their patients were female [5]. Four (50%) studies in the literature in Table 2 reported a higher number

of patients diagnosed with HM before RCC. NHL was the most common HM in the majority of these studies. In Dutcher and colleagues' review of 199 cases of RCC and HM in the same patient identified in the literature (n=173) and in their registry (n=26) between 1991 and 2016, an association between RCC and HM within families was observed, exemplified by 74 patients with RCC who had 95 family members with HM [8]. These authors suggested a genetic correlation between RCC and B-cell malignancies.

Our case series of 9 patients with concurrent RCC and HM confirms particular aspects in the literature in Table 2, such as the predominance of male gender (all 9 patients in our series) and NHL (7 cases in our series) as the most frequent HM. However, only 1 patient in our series was diagnosed with the HM before the RCC, as either simultaneous diagnosis of the RCC and HM (4 patients) or RCC diagnosis before the HM (4 patients) was more common."

Reviewer #1, Comment #8: "The discussion is interesting, but I suggest to focus in the immunotherapy."

Response to Reviewer #1, Comment #8: We have included a new paragraph in the Discussion (Page 13) which focuses on immunotherapy, as follows: "Strides have been made in cancer immunotherapy with the discovery of checkpoint inhibitors which effectively inhibit the immune system [22]. Programmed cell death 1 receptor (PD-1) signaling plays a role in encouraging cancer development and progression by boosting tumor cell survival [23]. It has been reported that blocking PD-1 signaling significantly promotes antitumor immunity, produces favorable clinical responses, and prolongs survival [23]. Developing antibodies that block PD-1 and programmed cell death receptor ligand 1 (PD-L1) have been investigated. The checkpoint inhibitors ipilimumab and nivolumab proved invaluable in the treatment of Case #8 as exemplified by the 7-month excellent response in this rare kidney cancer histology."

Reviewer #1, Comment #9: "Overall comments. The manuscript is interesting due the cases reported, however, the description of the cases is incomplete, and the discussion is weak. I suggest to the authors describe in detail immunologic theories, the possible relation to genetic heritage, to compare their cases with other reported cases and establish, as possible, recommendations about treatment and monitoring, stablish a possible theory or hypothesis about the predilection of masculine gender, and a hypothesis about HM and renal leiomyosarcoma in masculine gender."

Response to Reviewer #1, Comment #9: All of the descriptions of cases are now complete. We have strengthened by Discussion (Pages 9-11) by adding more detailed information regarding immunologic theories and the possible relation to genetic heritage, as follows: "A host of mechanisms has been reported as playing a role in developing concurrent RCC and HM. As the greatest number of patients with these combined conditions involves diagnosis of HM first [8,11], it has been proposed that immune dysregulation or breakdown of tumor surveillance associated with the lymphoma may lead to RCC [3,10]. An abnormal immune response may either precipitate lymphoma in patients whose RCC was diagnosed first or predispose a patient to developing both malignancies simultaneously [1,9,10]. As both lymphoma is a neoplasm of the immune system and RCC is a solid tumor that possesses an immune responsive behavior, the simultaneous occurrence of these diseases may be due to failure in tumor surveillance caused by the lymphoma that permits the RCC to develop [3]. In other cases, stimulation of the immune

system by the RCC may result in lymphocytic proliferation and clonal proliferation which may spur the development of the HM.

We propose that immune dysregulation may be a potential explanation for both RCC and HM occurring in one host, however, this is solely a theory and the exact mechanisms are not known. It may be partly explained by the fact that both RCC and HM are well-known to respond to immunotherapy although they may have different clinical aggressiveness based on histology and grade. Both malignancies may be monitored without treatment at times based on histology, grade, and clinical behavior. Indolent disease may start to progress quickly due to transformation of the tumor to a more agrressive type. It appears in some cases that the host's immune system may partially control the tumor growth resulting in "stable disease" without a need for treatment. In such cases, intrinsic or extrinsic immunosuppression may lead to tumor progression.

There is also an increased risk of RCC in patients with NHL that may be attributed to chemotherapy and radiation used in NHL treatment [2,3,11,12]. Additional etiologies for concurrent RCC and HM include viruses such as Epstein-Barr virus, H. pylori, and human T-lymphotropic virus-1 that have been implicated in lymphomas and carcinomas [2,8]. Interleukin-6 produced by RCC has been shown to stimulate the progression of MM [15]. A common genetic factor may also be involved in concurrent RCC and HM as common chromosomal abnormalities such as 3p and 17p deletions have been observed in both conditions [2,10,16,17]. In addition, *PTEN* germline mutations have been reported in hereditary RCC, and studies have described abnormalities of *PTEN* in T-cell and B-cell HM [8]. *PTEN* abnormalties as a common pathway for the development of RCC and HM in individuals or families remains to be elucidated [8]. The potential similar genetic components in these conditions necessitate a thorough investigation into family histories."

We have also added a new table (Table 2) that compares our cases to other reported cases in the literature and have described the other reported cases in the literature to our case series in the Discussion, as follows: "The phenomenon of concurrent RCC and HM has been reported in the literature, with a focus on gender, timing of the diagnosis of RCC and HM, and most common HM (Table 2) [1-5,8,10,11]. All except one of the studies in Table 2 documented a higher number of men with both conditions. Interestingly, in Tihan's and Filippa's study of 15 patients with coexisting RCC and malignant lymphoma, 11 (73%) of their patients were female [5]. Four (50%) studies in the literature in Table 2 reported a higher number of patients diagnosed with HM before RCC. NHL was the most common HM in the majority of these studies. In Dutcher and colleagues' review of 199 cases of RCC and HM in the same patient identified in the literature (n=173) and in their registry (n=26) between 1991 and 2016, an association between RCC and HM within families was observed, exemplified by 74 patients with RCC who had 95 family members with HM [8]. These authors suggested a genetic correlation between RCC and B-cell malignancies.

Our case series of 9 patients with concurrent RCC and HM confirms particular aspects in the literature in Table 2, such as the predominance of male gender (all 9 patients in our series) and NHL (7 cases in our series) as the most frequent HM. However, only 1 patient in our series was diagnosed with the HM before the RCC, as either simultaneous diagnosis of the RCC and HM (4 patients) or RCC diagnosis before the HM (4 patients) was more common."

We have provided recommendations about treatment and monitoring in the Discussion (Page 13), as follows: "Both RCC and HM may usually be monitored based on clinical and histological factors. RCC has risk stratification criteria (International Metastatic RCC Database Consortium [IMDC] criteria and Memorial Sloan-Kettering Cancer Center [MSKCC] criteria) which has been used extensively for offering treatment [24,25]. Watchful waiting may be offered in certain circumstances to patients with RCC. These patients generally have a favorable risk, low disease burden, and a single site of metastasis. Other factors such as metastatic site should be considered in cases of surveillance. Lung, adrenal, and pancreatic metastasis may potentially have a slower clinical course compared to liver and bone metastasis. Diligent monitoring may be performed for some asymptomatic patients with low-grade HM who do not have significant cytopenia."

We have established a possible theory or hypothesis about the predilection of masculine gender in the Discussion (Page 9): "We hypothesize that the predilection of male gender in concurrent RCC and HM may be due to the predominant gender in each cancer. In RCC, the male-to-female ratio is almost equal (1.2:1) in patients older than 70 years compared to a 2:1 ratio for patients ages 41 to 60 years old [13]. NHL is significantly more common in males [14]. The lower rate of NHL among females may be explained by direct effects of estrogens on lymphoma cell proliferation or by its effect on anti-tumor immune response [14]. The higher prevalence of males in concurrent RCC and HM may be attributed to more males compared to females affected in both RCC and HM."

Finally, we have established a hypothesis about HM and renal leiomyosarcoma in masculine gender in the Discussion (Page 12): "Case #8 was diagnosed with the exceedingly rare and aggressive leiomyosarcoma of the kidney which accounts for only 0.12% of renal malignancies and is usually detected in women [18-20]. The cause of female predominance is not fully understood, however, it has been suggested that some malignancies are associated with genes located on X chromosomes that avoid X-inactivation [18,21]. Interestingly, a male predominance has been reported with concurrent RCC and HM, while renal leiomyosarcoma is more common in females. The diagnosis of renal leiomyosarcoma in a male with a simultaneous lymphoma makes our case more unique."

Reviewer #1, Comment #10: "Final comments This manuscript is interesting and describes and important series of cases, however I think it has several lacks that the authors must review and resolve. Thus, I recommend this manuscript for major changes."

Response to Reviewer #1, Comment #10: We are pleased that the reviewer finds our manuscript interesting with an important series of cases. We have significantly revised the entire manuscript and have incorporated all of the reviewer's suggestions.