Author's response to reviews

Title: Severe paraneoplastic hypereosinophilia in metastatic renal cell carcinoma

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Author's response to reviews: see over
Dear Dr. Henderson,

we submit our revised manuscript entitled “Critical paraneoplastic hypereosinophilia and metastatic renal cell carcinoma” by Tilman Todenhoefer, Stefan Wirths, Claus Hann von Weyhern, Stefan Heckl, Marius Horger, Arnulf Stenzl, Lothar Kanz, and myself to BMC Urology for editorial consideration.

We have carefully looked at the reviewers’ comments and made the following changes in the manuscript.

Reviewer 1:

The manuscript entitled „Severe paraneoplastic hypereosinophilia in metastatic renal cell carcinoma“ claims to report the first case of paraneoplastic hypereosinophilia in a patient with renal cell carcinoma. This is an interesting phenomenon, physicians treating those patients with sophisticated drugs should be aware of. However, treatment options are limited, in particular when trying to balance antineoplastic drugs with immunosuppressive approaches. Respective patients are in a fatal situation where oftentimes even mid-term oncologic benefit is difficult to achieve as shown here. Several concerns that need to be addressed:
1) What did the authors plan for the patient subsequently after nephrectomy with this pT4, pNx, M1, L0, V1, G3 tumor? I imagine, that around day 20-28 a sort of targeted concept should have been prepared?

The patient was discussed in an interdisciplinary tumor board and was recommended to be treated with systemic therapy with sunitinib. (This information was added to the case presentation)

2) How was this patient stratified according to MSKCC or Motzer criteria? Was not this a high risk patient?

According to the Motzer criteria, this patient was stratified as intermediate risk at time of diagnosis and time of readmission to our hospital.

3) What was the rationale for initial sunitinib first line approach in that young patient?

The European Association of Urology recommends sunitinib as first line agent in patients with metastatic renal cell carcinoma and low or intermediate risk (according to MSKCC criteria).

4) The authors state that sunitinib had to be replaced by temsirolimus because of swallowing. Did this patient need parenteral nutrition or did he selectively swallow sunitinib? What about other peroral medications? The justification for the therapy switch sounds awkward.

The patient required parental nutrition due to insufficient swallowing. Complete medication was switched from oral to intravenous.

5) I have the impression that temsirolimus would have been the appropriate first line treatment for this patient.

According to the guidelines of the European Association of Urology, sunitinib is the treatment of choice for patients with intermediate risk.

6) In Fig 2 sunitinib is re-initiated after 6 infusions of temsirolimus, this is not
stated in the text and seems not plausible. Why did the authors do so?

Sunitinib was reinitiated on request of the patient and his wife to continue with oral therapy to avoid weekly visits at the hospital to receive temsirolimus. An explanation was added to the text to clarify the reason for this switch.

7) The retroperitoneal mass was finally defined as what? After first drainage no information of tumor cells is given. No cytology? Was it „just“ an abscess? Later the authors write about a CT scan performed 2 weeks after the drainage of the fluid collection and declare the process as massive progression of the retroperitoneal tumor mass in the surgical bed. Has it already been a local recurrence when first draining? This has to be clarified.

Retrospectively, the retroperitoneal mass has to be considered as retroperitoneal tumor mass. Microbiology of the drained fluid did not show any growth of bacteria or yeast. Creatinin of the fluid was equivalent to serum creatinine. Amylase and lipase in the drained fluid were without pathological findings. Although cytology was negative, the retroperitoneal mass has to be considered as tumor retrospectively.

8) A table stating the performed diagnostic/therapeutic activities would help the reader to better perceive the clinical course.

In figure 2, most important events are combined with dosage and duration of systemic treatment. We’re afraid that a table would not provide a sufficient overview of the course of disease and treatment. The retroperitoneal fluid mass and drainage of it were added to the figure as important event.

Reviewer 2

This is an interesting and well written case report of „severe paraneoplastic hypereosinophilia in a patient with metastatic renal cell carcinoma. Minor comments:
through out the text some grammatical changes needed, e.g. 'was set on'. should be changed to started chemotherapy.

The whole paper was revised for grammatical errors. All obvious errors were corrected

reference ranges for all lab values

Reference ranges for all lab values were added.

- what was the level of eosinophiles prior to surgery and have these changes be considered at this point?

At primary diagnosis (prior to surgery), white blood count revealed 19550 leukocytes/µl with 16% eosinophils (mentioned in the test). As 7 days after primary diagnosis (1 day before surgery) WBC dropped to 11000, no further attention was turned on the WBC and the increased eosinophils until readmission 4 weeks later.

Reviewer 3:

1. The authors should clarify, whether the tumor really "infiltrated the vena cava" or whether they mean the presence of a tumor thrombus (level ?). I suggest to show a representative CT-scan of the primary, either as an additional figure or as a replacement of Figure 1, which appears to be of minor interest. Moreover, the status of the resection margins following radical nephrectomy is missing and should be added to the TNM-status.

The initial CT scan showed a level I cava thrombus. A preoperative CT scan was added as a figure (unfortunately no coronar reconstructions are availabe, therefore a transversal image was added). The resection margin status was added to final pathology (Rx).

2. To better characterize the patients risk profile, the authors are encouraged to state the Motzer Score or Heng criteria.

The risk profile of the patient according to the Motzer (MSKCC criteria) was added.
3. I would suggest, that the therapeutic concept for cytoreductive treatment of leucocytosis and hypereosinophilia was developed in close collaboration with medical oncologists. If so, the authors should mention that.

Cytoreductive therapy was administered in the department of medical oncology. A sentence was added to the text mentioning the transfer to medical oncology.

4. The authors do not give any explanations or suggestions, why the count of WBCs steadily increased following the resection of the primary. This aspect should be discussed, at least briefly, in the discussion section of the manuscript.

Following the resection of the primary tumor, the leukocyte count increased from 11000 preoperatively to 15500 on day 5. However, with a downward trend and a WBC of 14360, the patient was discharged on day 7. Until day 29, no WBC was performed. As Figure 2 might lead to misinterpretation due to a WBC curve with connected time points, this important information was added to the text. Furthermore, a sentence was added to the discussion section: „However, as a steady increase of leukocytes was observed after resection of the tumor with necrotic areas, tumor necrosis cannot be regarded as the only promoter of increasing eosinophils in the present case and other sources for cytokines promoting hypereosinophilia are probable.“

Reviewer 4:

1) Hypereosinophilia is observed in diverse conditions. In fact the authors briefly described as “Several tests were performed to rule out non-cancer causes………., which remained all negative” (Case presentation and management), but this issue is crucial. Physicians often devote much effort but actually have lots of difficulties to identify the underlying disease. Besides, various disorders are likely in such a reduced general conditions (e.g. drugs use, infections). The authors should specify how the differential diagnosis was made.
A convincing account will be also informative to readers (physicians). Otherwise the term “paraneoplastic” is not appropriate.

A couple of tests was performed to rule out other possible causes of hypereosinophilia. As the interval between readmission with almost 30000 WBCs and last intake of oral medication (levofloxacin) was 14 days, a drug induced hypereosinophilia is not probable. Mast cell tryptase determination in serum did not reveal any abnormality compatible with an allergic reaction. Complex analysis was performed by a specialist in this field (Dr. A. Reiter, Mannheim, Germany) to rule out FIP1L1/PDGFR receptor mutations as sign of hypereosinophilic syndrome. Furthermore, FACS analysis of the peripheral blood did not show any aberrant lymphocytes as sign of lymphoproliferative hypereosinophilic syndrome. Testing for protozoa and helminths were without pathological findings. Serology for candida and aspergillus were negative. Rectal swob, urine culture, blood culture and sputum were negative. Bone marrow aspirate did not show a hematologic malignancy. More detailed information was added to the section mentioning the tests performed to rule out other causes of hypereosinophilia.

2) The authors should note the past medical history (completely disease-free?). This will be clue for the above differential diagnosis and in clarifying what happened along with the development of hypereosinophilia.

The patient did not have any chronic disease or surgeries in past medical history. The patient did not take any regular medication. This information was added to the case presentation.

3) How were organ involvements associated with hypereosinophilia other than the brain and heart? In general, lung (except for tumor metastasis) and skin are the sites of predilection.

A CT of the chest only showed progressive metastases without changes consistent with organ involvement of hypereosinophilia. No skin changes were recorded. Therefore, heart and brain were the main organs involved by the hypereosinophilia.

4) Is the left ventricular asynergy a new event? Was there a temporal change in electrocardiogram (comparison with the admission time)?
In past medical history, no transthoracal echokardiography was performed. Therefore, no statement can be done whether the asynergy is a new event. In the corresponding ECG, sinus tachycardia and ventricular extrasystoles (Lown II) were recorded, which were not present in the ECG preoperatively. This information was added to the case presentation.

5) How was the bone-marrow examination? The results (if available) might be helpful to rule out hematological malignancies and provide a deep insight into the pathomechanism of hypereosinophilia just as the authors documented in discussion.

Bone marrow analysis did not reveal any signs of a hematologic malignancy

We hope that with these modifications our contribution will now be considered suitable for publication in your journal.

On behalf of all the named authors, yours sincerely,

Christian Schwentner, MD
Professor of Urology