Author's response to reviews

Title: Extrarenal nephroblastomatosis in children: A report of two cases

Authors:

Yi Wu (170330856@qq.com)
Xue ming Zhu (xueming_zhu@aliyun.com)
Xing dong Wang (13914073627@163.com)
Hang zhou Wang (wanghangzhoudr@126.com)
Xu Cao (cao_xu1982@163.com)
Jian Wang (wj196312@vip.163.com)

Version: 3 Date: 15 September 2014

Author's response to reviews: see over
Cover Letter

Dear Editor and Reviewers:

Thank you for your letter and for the reviewers comments concerning our manuscript entitled “Extrarenal nephroblastomatosis in children: A report of two cases” (MS: 1531012475133330). These comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made corrections which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer’s comments are as flowing:

Reviewer: Gordan M Vujanic

Reviewer’s report:

This is a nicely written paper presenting two cases of a relatively uncommon lesion -extrarenal nephroblastomatosis. The authors say that they have identified two cases in their 10-year material -it would be interesting to know how many cases of Wilms tumour they have had in the same period.

There have been 25 cases of Wilms tumour in this period but none of them is extrarenal.

Major points:

line 142: "the distinguishing characteristics of nephroblastoma are frank atypia, atypical mitoses and marked pleomorphism" -it is not quite clear what is meant by this, are the authors listing histological features of anaplasia to which they refer in the following sentence? If so, than the diagnostic features of anaplasia are not precisely listed as they include atypical mitoses, marked nuclear enlargement and hyperchromasia. Anyway, the features they have listed as "characteristics of nephroblastoma" are not quite right, or the wording of this sentence is not good, so should be rephrased.

We have revised the sentence to avoid misunderstanding. Atypia is a diagnosis standard of nephroblastoma, but anaplasia is not necessary. Only 5% cases occurs anaplasia, indicating poor differentiation.

line 146: "... and moderate pleomorphism, but no atypia." -the rests do not show any pleomorphism and if it is present, than the diagnosis of Wilms tumour is more likely.

The reviewer considered that rests do not show any pleomorphism, but in the other opinion, high mitotic rates and moderate pleomorphism can also be found in proliferative nephrogenic rests, which is difficult to distinguish to Wilms tumor[1, 2].

line 175: "In the case of renal nephrogenic rests, however, approximately 40% are associated with Wilms tumor." -it is actually the other way around, ~40% of unilateral Wilms' tumours are associated with nephrogenic rests. The incidence of nephrogenic
rests not associated with Wilms tumour is not known.

We’ve rephrased the sentence at the right description.

line 179: "some nephrogenic rests are associated with teratoma and therefore, have a poor prognosis [27]; these lesions require surgical treatment with additional chemotherapy." -this is new to me, presumably, the authors want to say that some extra-renal nephrogenic rests may be associated with teratoma? If so, it is still inaccurate to say that such cases require additional chemotherapy teratoma in children, even the immature ones, are treated with surgery only, and I don't think that there are any accepted protocol which advise chemotherapy for teratomas associated with nephrogenic rests. In the quoted reference (27), the authors only comment that in some cases chemotherapy but do not recommend it routinely.

Combining the comments of the two reviewers, we’ve deleted the “additional chemotherapy” part to make the conclusion to be drawn directly from the two presented cases.

Minor points

line 134: "Differential diagnosis between benign extrarenal nephroblastomatosis and malignant nephroblastoma is mandatory..." -there is no benign nephroblastoma, so the word malignant should/could be replaced with "extra-renal"

We have deleted the words “benign and malignant” for there is no benign nephroblastoma or malignant nephroblastomatosis.

line 140: "on cytological examination..." presumably, the authors wanted to say "on histological examination.."?

We have replaced the word cytological with histological.

line 265-274: Figures legends are not what they should be, describing what is presented in the figures, we do not need to know which staining was used (that can go in the brackets, with the magnification) but what we are supposed to see in them. I am not entirely convinced that Fig 2C shows a blastemal component.

We have revised the legends and changed the Fig 2C according to the reviewer’s comments. However, the case didn’t show obvious blastemal component, thus the Fig 2C we illustrated contained only a little blastemal component.

line 155: "In the second patient, the ectopic nephrogenic rests were thought to have originated from mesonephric or metanephric tissue." -what about the first case, is it not the same possibility?

We have deleted the phrase "In the second patient" because all the nephrogenic rests were thought to have originated from mesonephric or metanephric tissue, not only this case.
Reviewer: Lydia Pecker

Reviewer's report:

1. Major Compulsory Revisions

* Abstract of case reports should be revised to 1) introduce in the first sentence why two cases of extra renal nephroblastomatosis are of interest and importance to the reader. Next, the two cases should be more briefly summarized. For instance, since each patient underwent surgical resection observation as follow-up, this may be stated in one sentence. Finally, the conclusions of the abstract appear to stray from the information reported in the cases. As your cases are neither extrarenal nephrogenic rests, nor associated with teratoma, I am confused about why these are the ultimate conclusions of your abstract. Conclusions should direct the reader to the instructive nature of the reported cases and may highlight any future work indicated by the unknowns associated with extrarenal nephroblastomatosis.

We have revised the abstract according to the comments, highlighting the importance of the cases and simplifying the case presentation and conclusion. Otherwise, it is remarkable that extrarenal nephroblastomatosis we reported here are also named as extrarenal nephrogenic rests (ENR).

* Citations in this paper are thoughtful and extensive. However, I am left wondering: Why do two additional cases of extrarenal nephroblastomatosis without unusual clinical sequelae or dramatic presentations warrant publication? The authors are should highlight the educational value, clinical importance or management challenges raised by the cases they identified. Nephrogenic rests usually occur as perilobar and intralobar lesions in the kidney and, rarely, in ectopic sites. Heterotopic NRs have been reported in several sites, but here we reported the new sites that one was in testis in the inguinal canal and the other in spinal canal at the thoracolumbar region. These case reports replenish to the literature of pediatrics and remind the pathologists to consider NRs when masses are found in these positions.

* Given the association of Wilms Tumor with multiple genetic syndromes, the authors should remark on the overall health of the two patients identified. Were these children with cancer predisposition syndromes? Did they have stigmata of Beckwith Weideman, Denys Drash or WAGAR?

The two patients were underwent the regular examinations before surgeries, and there was no evidence of neurologic, ocular, abdominal wall or genitourinary abnormalities, hemihypertrophy, organomegalies, or other tumors. In the manuscript, we have mentioned the results at Line 73 and Line 99.

* Were pathology specimens tested for genetic testing for WT1 or WT2 mutations? Would this information, if available, have changed management?
No, we didn’t test the WT1 or WT2 mutations. Although it is reported that NRs accompany with Wilms tumor were associated with WT1 mutation[3], and intralobar NRs were more commonly associated with WT1 (11p) gene mutations, and syndromes such as Denys-Drash and WAGR[4], our decisions were not depend on the WT1 or WT2 mutations but on the subclinical benign facts.

* Both patients were managed without adjuvant chemotherapy or radiation. On what basis was this decision made?

In conclusion, we summarized the management on this nephrogenic rests subject including surgery and follow-up for its subclinical. Otherwise, proliferative universal NRs and NRs associated with teratoma require consider additional adjuvant treatment for their potential malignancy.

In our two cases, the nephrogenic epithelial elements (glomeruli, tubules) had differentiated to a rather advanced degree, and rare mitoses with no atypia were found scattered within the dense fibrous tissue, indicating a benign neoplasm. The diagnosis of teratoma was also excluded due to the lack of other teratomatous non-nephrogenic tissues. Thus we decided to choose the conservative therapy.

* Conclusions must be revised to be drawn directly from the two presented cases. We have revised the conclusion according to the comment.

2. Minor Essential Revisions

* Lines 71-72 seem to conflict with lines 80-81. Was the mass invasive to the testicle or not?

The mass attached to the testis was unseparated. On histological examination, the nephrogenic rests was intervened in the testicular tissue but no definitive invasive component was found.

3. Discretionary Revisions

Management of nephrogenic rests and extrarenal nephroblastomatosis is a clinical challenge because of the concern for malignant transformaiton. The interesting finding of testicular nephroblastomatosis in an undescended testicle, which also carries a risk for malignant transformation might be explored.

The authors are encouraged to present the pathology findings once and to tie these findings more closely to clinical concerns and management decisions.

Extrarenal nephroblstomatosis are reported in everywhere, such as lumbosacral area, adrenal gland, thorax, colon, heart, especially the retroperitoneum and inguinal region. Pathologists should consider extrarenal nephroblastomatosis when observe to undifferentiated blastemal tissue and nephrogenic epithelial elements (glomeruli, tubules). Malignant neoplasm including nephroblastoma must be excluded. Otherwise, mitosis rates must be concerned for proliferative nephrogenic rests are required adjunctive therapy.
Thank you very much for your good comments. We tried our best to improve the manuscript and made some changes. These changes will not influence the content and framework of the paper. We appreciate for Editors and Reviewers’ warm work and hope that the correction will meet with approval.

Sincerely,

Xueming Zhu
Department of Pathology, Soochow University Affiliated Children's Hospital, Jiangsu 215003, China.
Address: 303 Jingde Road, Suzhou, Jiangsu, 215003, China
E-mail: xueming_zhu@aliyun.com
Tel: +86 0512 67786712
Fax: +86 0512 65224492

Reference