Author's response to reviews

Title: CD 9 and vimentin distinguish clear cell from chromophobe renal cell carcinoma

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Author's response to reviews: see over
Dear colleagues:

Thank you for your review of our manuscript “CD9 and vimentin distinguish clear cell from chromophobe renal cell carcinoma” and for the opportunity to resubmit it for publication in *BMC Clinical Pathology*. We appreciate your suggestions and have altered our manuscript to reflect them. Our response to the specific comments is as follows:

- **Classification of granular cell carcinoma and sarcomatoid renal cell carcinoma:** Granular cell carcinoma and sarcomatoid renal cell carcinoma are now grouped with renal cell carcinoma, unclassified, in accordance with the current WHO classification.

- **Poorly differentiated carcinomas:** Poorly differentiated carcinomas are now grouped with renal cell carcinoma, unclassified, in accordance with the current WHO classification.

- **Papillary renal epithelial neoplasm:** On closer examination, we have found this specimen to be a type II papillary renal cell carcinoma (pRCC). It is now described as such.

- **Expression of CD9 and vimentin in oncocytoma:** The staining patterns of CD9 and vimentin in oncocytoma are now described in a paragraph in the results section. We have also added a paragraph in the discussion describing the difficulty differentiating oncocytoma and chromophobe renal cell carcinoma (chRCC) and how this relates to our findings.
• **Novelty of study:** CD9 was first described as a marker of renal cell carcinoma by Kuroda et al in a 2001 paper in *Human Pathology*. These authors studied 66 clear cell renal cell carcinoma (ccRCC), 5 chRCC, 2 oncocytoa, 13 papillary renal cell carcinoma (pRCC), and 4 collecting duct carcinomas and found that 47% of ccRCC, 100% of chRCC, 100% of oncocytoa, 100% of pRCC, and 25% of collecting duct carcinomas exhibited positive staining for CD9. They concluded that CD9 was a sensitive but nonspecific marker of chRCC and pRCC. To our knowledge, no other reports of CD9 expression in chRCC and ccRCC have been published to date.

We have studied a much larger set of tumors than the prior authors, including 249 ccRCC, 25 chRCC, 17 oncocytoa, 38 pRCC, and 47 urothelial carcinomas, and came to markedly different conclusions. 6.1% of ccRCC, 100% of chRCC, 56.3% of oncocytoa, and no pRCC or urothelial carcinomas in our tumor set stained positive for CD9, suggesting that CD9 is indeed a highly specific marker for chRCC. Thus, CD9 may have significantly greater clinical utility in the diagnosis of RCC than previously believed.

• **Role of CD9 in kidney biology and malignancy and its potential as a therapeutic target:** Three paragraphs have been added to the discussion in which we review these topics.

We continue to be excited by our findings and look forward to your review of our revised manuscript. Please do not hesitate to contact any of us if we can offer further information.

Sincerely yours,
James D. Brooks, MD