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Letter to the Editor

A distinct expression pattern and point mutation of c-KIT in papillary renal cell carcinomas

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To the editor: I read with interest the article by Lin *et al*[1] concerning the expression of KIT in renal cell carcinomas. Their findings of membranous immunoreactivity for KIT in chromophobe renal cell carcinomas and focal cytoplasmic immunoreactivity in normal renal tubular cells are in keeping with ours[2] and two other recently published studies.[3,4] However, only Lin *et al* observed a strong cytoplasmic KIT positivity in papillary renal cell carcinoma. Since the cytoplasmic reactivity for KIT, in contrast to the consistent membranous reactivity, has been shown to vary greatly with sources and dilutions of antibodies, as well as the heat-induced epitope retrieval (HIER) methods,[5] we suspect the discrepancy may also be related to a technique variation.

The major difference we find between the study of Lin *et al* and ours is that Lin *et al* used ethylenediaminetetraacetic acid (EDTA) as HIER buffer while we used citric acid. In order to reproduce the results of Lin *et al*, we performed the KIT immunostain exactly following the methods described in their paper. Then we compared the results with our previous ones with citric acid HIER. When citric acid was used, a minor proportion (4/25) of papillary renal cell carcinomas revealed a very faint cytoplasmic reactivity, which we used to consider as being negative. The reaction became more intense when EDTA was used, with around half of papillary renal cell carcinomas (12/25) exhibiting obvious granular cytoplasmic positivity in our cases. The membranous immunoreactivity in chromophobe renal cell carcinomas was not altered. Figure 1 depicts the sharp contrast of the two immunostains on the same field of step sections of one papillary renal cell carcinoma.

Because the cytoplasmic immunoreactivity could be blocked by blocking peptides,[1] it is unlikely caused by nonspecific adsorption. As Lin *et al* hypothesized, it may be a mutated KIT protein. Their finding of intron 17 mutation in papillary renal cell carcinomas raised such a possibility.[1]

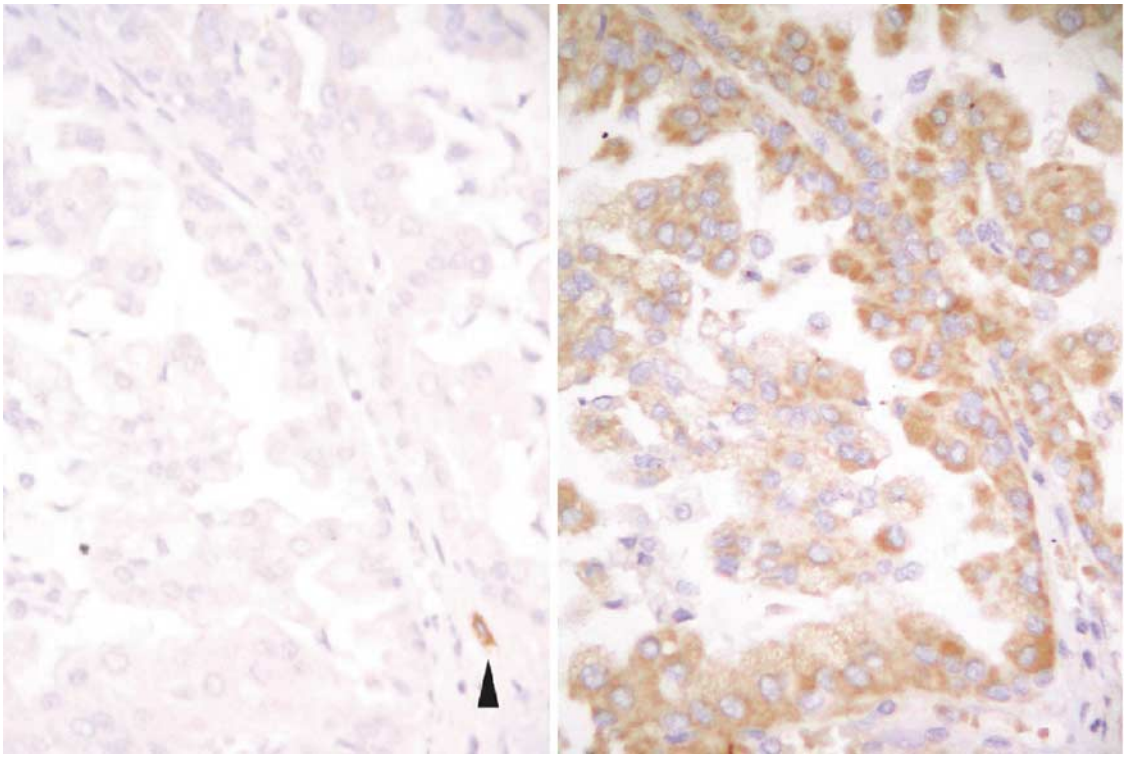

Figure 1 With citric acid HIER, papillary renal cell carcinoma rarely exhibited faint cytoplasmic immunoreactivity for KIT (left). With EDTA pretreatment, the papillary renal cell carcinoma showed strong granular cytoplasmic reactivity (right). The arrow indicates a mast cell.

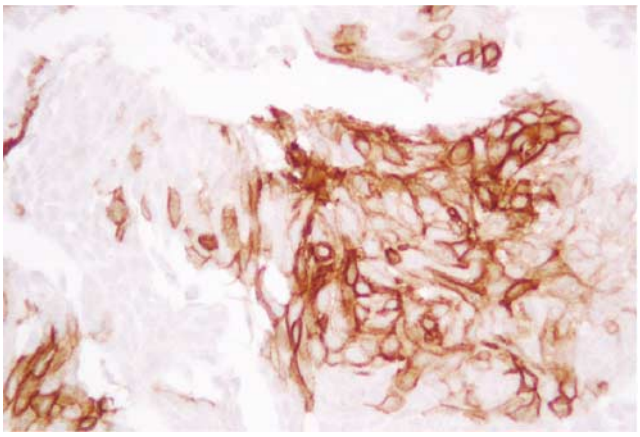

Figure 2 Heterogeneous membranous immunoreactivity for KIT in papillary urothelial carcinoma.

However, Lin *et al* and we could not identify any mutation within the juxtamembranous and tyrosine kinase domains in all cases.[1,2] The other possibility that cannot be confidently dismissed is that the antibody crossreacts with another unknown cytoplasmic epitope that bears structural similarity with KIT hence it can also be blocked by the blocking peptides. HIER affects the antigenicity of the cytoplasmic epitope, which is probably expressed at a lower level compared with the true membranous expression of KIT, given that it can only be unmasked by EDTA. Even with the same staining condition, the overall positive rate in our cases is still lower. Other factors such as fixation may play a role. We think using frozen sections to eschew the HIER would be very helpful to address the issue.

Finally, for practicing pathologists who want to employ the KIT immunostain to differentiate papillary renal cell carcinoma from papillary urothelial carcinoma as Lin *et al* recommended, we would like to offer our experience. In our limited cases of papillary urothelial carcinoma, four of 11 cases revealed heterogenous membranous positivity for KIT (Figure 2).[2] Consequently, one must be careful in discerning the different staining patterns. The study of Lin *et al* does demonstrate the tricky aspect of immunohistochemistry. The seemingly simple technique, which many pathologists resort to almost at a daily basis, is not simple at all.

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