Immunohistochemistry Stain and Molecular Genetic Study of Hemangioblastoma: An Indication of Anti-VEGF Target Therapy

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BACKGROUND

Hemangioblastomas (HB) are uncommon, slow-growing tumors of the central nervous system without available target therapy. Hemangioblastomas occur both sporadically and as an important component of von Hippel-Lindau (VHL) disease which is associated with clear cell RCC (ccRCC). Acutely, HB and ccRCC have some similarities at morphological level. Here, we would like to investigate sporadic HB by IHC stains and molecular genetic approach to explore the possibility of anti-VEGF target therapy which is suitable for ccRCC.

DESIGN

25 cases of sporadic HB were collected. For IHC stains, tissue microarray (TMA) was constructed. IHC stains of Pax8, CA9 and inhibin were applied to TMA slides. The UroGenRA™-Kidney Array-CGH Assay was used to evaluate molecular genetic changes in HB. This assay detects copy number alterations associated with the four main renal tumor subtypes, including loss of the Von Hippel-Lindau (VHL) gene in ccRCC.

Fig 1: Hemagioblastoma: a)CA9 (25/25); b) PAX8 (0/25); c) Inhibin (10/25)

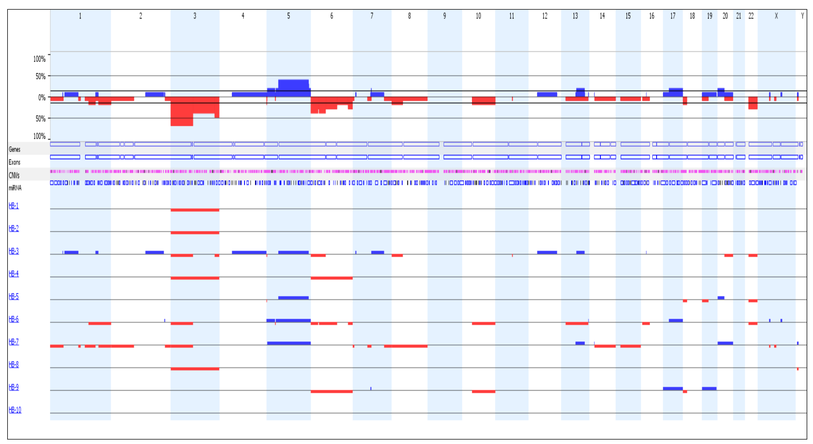

Fig 2: Copy number alterations detected across the genome by UroGenRA™ –Kidney array-CGH assay for all the 10 HB specimens. Gains are indicated in blue and losses are shown in red.

RESULTS

IHC stains have been applied to 25 cases. All 25 cases of HB showed strongly, diffuse membrane stain of CA9 (identical to ccRCC); completely negative for Pax8 (renal marker). Only 10 cases were positive for inhibin. For the 10 cases of HB which underwent UroGenRA™-Kidney Array-CGH assay, 9 cases presented several genomic changes and 1 case exhibited no copy number change. Among the 9 cases with multiple genomic alterations, 7 cases showed partial or entire chromosome 3 deletion spanning *VHL* gene locus and 4 cases displayed partial or entire chromosome 6 deletion, both these alterations are commonly observed in HB cases.

CONCLUSIONS

Our study demonstrated that hemangioblastoma are strongly positive for CA9 which is identical to that in ccRCC and indicates dysregulation of VHL-pseudohypoxia signal pathway. In addition, 70% of HB had chromosome 3 deletion. These results suggest that some cases of HB had genetic change similar to that of ccRCC and HB would be suitable of anti-VEGF target therapy. However, we could not identify loss of VHL gene in 30% of HB cases. This indicates that those HB may use other molecular mechanism for down regulation of VHL gene, such as point mutations or promoter region hypermethylation which warrant for further study.