Case Report

A Unique Pair of Monozygotic Twins with Concordant Clear Cell Renal Cell Carcinoma: A Case Report

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Abstract

Introduction: Genetic predisposition to clear cell renal cell carcinoma (ccRCC) has been linked to disorders such as von Hippel-Lindau (VHL) syndrome. While twin research is a classic approach for elucidating genetic and environmental contributions to disease, no monozygotic twin-pair concordant for ccRCC in the absence of VHL syndrome has been previously reported in the literature or in major twin registries. Clinical Picture: We describe a unique monozygotic twin-pair concordant for ccRCC, with discordant but early ages of onset of 25 and 38 respectively. Cytogenetic studies and direct sequencing for *VHL* gene mutations in the second twin proved unremarkable. Conclusions: This is the first reported case of monozygotic twins concordant for ccRCC in the absence of *VHL* gene mutation. The early yet discordant, age of onset of disease in both twins suggests both genetic and environmental contributions to ccRCC.

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Key words: Gene-environment interaction, Kidney cancer, von Hippel Lindau syndrome

Introduction

Studies of monozygotic and dizygotic twins represent an important approach in estimating the relative contributions of genes and environment to the development of various cancers and disease in general. However, remarkably and almost curiously, there has been no monozygotic twin-pair concordant for clear cell renal cell carcinoma (ccRCC) reported in the literature in the absence of VHL syndrome. Combined data from the Swedish, Danish and Finnish twin registries including 44,788 twin pairs reported that no twin-pair exhibited concordance for kidney cancer.[1] We describe in this report a unique pair of concordant monozygotic twins with discordant-onset ccRCC without *VHL* gene mutation that to our knowledge is unique in the literature.

Case Report

Mr. A and Mr. B were monozygotic twins with no family history of cancer. At the age of 25, Mr. A presented with a 1-month history of painless haematuria, and a work-up revealed a localised 9 cm lesion in the upper pole of his left kidney, with invasion of the renal vein and pelvis, with no evidence of distant metastases. He underwent an open left radical nephrectomy, and histological examination of the resected specimen showed ccRCC, with Fuhrman grade 2 to 3 nuclear cytology (Fig. 1). Unfortunately, he relapsed 3 months after surgery with multiple liver metastases and died 2 months thereafter from progressive disease.

Mr B, his twin, was subsequently placed on regular follow-up, and at the age of 38, a 4-cm mass in his right kidney was detected on routine annual ultrasound screening. He underwent a laparoscopic left radical nephrectomy, and pathologic examination revealed a well circumscribed ccRCC, Fuhrman grade 3, at the upper pole of the left kidney (Fig. 2). The tumour was confined within the kidney with no lymphovascular invasion or necrosis. A strong histologic similarity was noted with the tumour from Mr. A, both high-grade tumours showing clear cells in a sheet-like distribution and alveolated nests. After 24 months of follow-up, he remains well and free from relapse.

At this point, Mr. B was referred for genetic counselling

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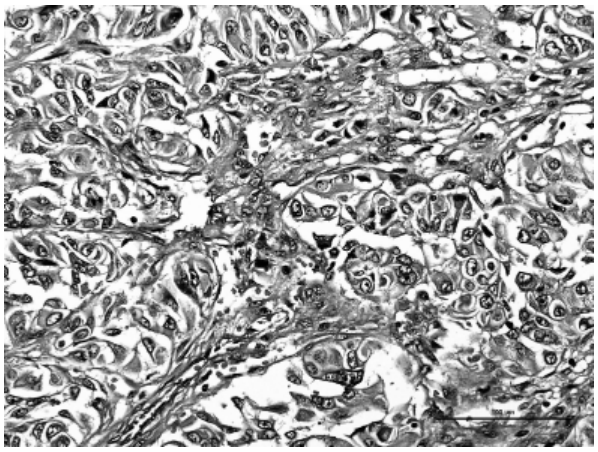

Fig. 1. Microscopic appearance (20x) of grade 3 clear cell renal cell carcinoma from Mr. A's tumour.

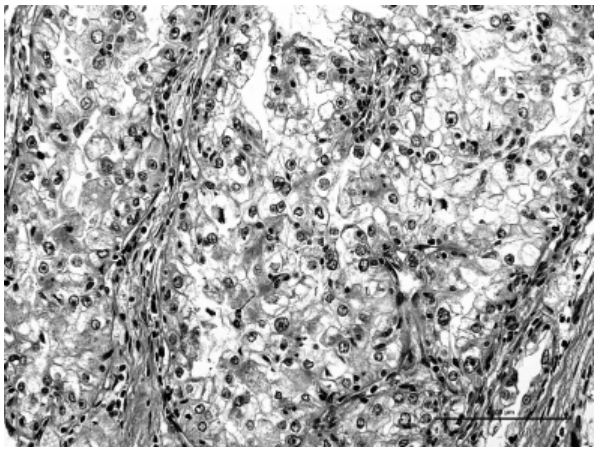

Fig. 2. Microscopic appearance (20x) of grade 3 clear cell renal cell carcinoma from Mr. B's tumour.

at the National Cancer Centre Singapore. Routine chromosome karyotyping yielded a male karyotype with no apparent chromosomal abnormalities. In particular, no rearrangements of chromosome 3 were shown. DNA extraction was performed from peripheral blood leukocytes from 10 mL of peripheral blood, and direct sequencing was performed for VHL mutation. The quality of tissue DNA from Mr. A's tumour was inadequate for sequencing. Primer sequences and protocols are available upon request. No *VHL* gene mutation was found. Patient consent for publication was obtained.

Discussion

Kidney cancer accounts for approximately 3% of adult malignancies, with renal cell carcinoma (RCC) comprising more than 90% of all primary renal tumours. The clear cell variant of RCC accounts for approximately 70% to 80% of the main histological subtypes. It is estimated that about 54,390 new cases of kidney cancer (33,130 in men and 21,260 in women) will be diagnosed in the United States in 2008, and about 13,010 people (8100 men and 4910 women) will die from it.[2]

While the majority of RCC are sporadic, a small proportion of less than 4% are hereditary.[3,4] The identification of the predisposing genetic alterations associated with the various histologic subtypes such as *VHL* gene mutation and ccRCC has provided insight into the various mechanisms of renal tumorigenesis. To date, multiple familial syndromes associated with the various histological subtypes of RCC have been identified. In particular, germline gene mutations identified in familial ccRCC have included the *VHL*, *BHD*, *TSC1* and *SDHB* genes, with germline chromosome 3 rearrangements being identified in an additional set of families.[5,6]

Twin studies have traditionally been used to determine relative contributions of genetic and environmental factors towards cancer development, and discordance of phenotype between monozygotic twins has been of biological interest. Curiously, unlike many other cancers, no concordant pair for kidney cancer has been reported in the literature. A large multinational survey of twins did not yield any such pair as well.[1]

Ours is the first reported case of monozygotic twins concordant for ccRCC without *VHL* gene mutation. In this case, a genetic link is suggested by the early age of onset in the 2nd and 3rd decade of life, and the morphological similarity of both tumours. With regard to the issue of discordant timing of onset for cancer in a monozygotic twins, a recent report of monozygotic twins discordant for acute lymphoblastic leukaemia characterised by a chromosomal translocation generating a *TEL-AML1* fusion gene has shed light on the pre-cancerous niche.[7] Through the examination of this twin pair, the authors derived insights into a possible developmental relationship between an early preleukaemic cell with the *TEL-AML1* fusion and cancer-propagating cells downstream of the initial oncogenic event. Our twin pair presumably similarly shared a common predisposition responsible for the development of ccRCC. Therefore, we hypothesize that an underlying common genetic rather than a common environmental cause is probably responsible in view of the early onset of disease of the first twin pair. The different timing of development of RCC likely reflects a second insult; the different timing implies an underlying environmental cause.

Although a wild-type *VHL* gene sequence, a normal karyotype and no other stigmata of a multi-cancer syndrome was found, we cannot exclude the possibility that the mutation of a recognised gene may underlie these twins.

Nevertheless, the discordant timing of cancer in both twins, as well as the absence of other features of a multi-cancer syndrome argue against the predominance of a genetic cause. It is possible that other susceptibility genes with low penetrance may exist,[8] with gene-environment interactions playing a major role in carcinogenesis. Consistent with this argument, a single report of concordant ccRCC in a monozygotic twin-pair linked to the VHL syndrome was identified in the Chinese language literature.[9] Both twins manifesting cerebellar haemangioblastoma and ccRCC at the same age of 40, as would be expected with a syndrome with a predominantly genetic association.

Conclusion

In summary, we report a unique set of monozygotic twins concordant for ccRCC, without *VHL* gene mutations. We surmise the presence of both genetic and environmental contributions in the pathogenesis of ccRCC in this twin pair, based on early but discordant onset of ccRCC in both twins.

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