

Oncology

Renal Cell Carcinoma in a Young Adult – Do We Need Further Investigations?



Matthias Walter^{a,b,c,*}, Christian Wetterauer^c, Elisabeth Bruder^d, Ellen C. Obermann^d, Svetozar Subotic^e, Stephen Wyler^a

^a Department of Urology, Cantonal Hospital Aarau, Aarau, Switzerland

^b SCI Center and Research, Neuro-Urology, Balgrist University Hospital, Zurich, Switzerland

^c Department of Urology, University Hospital Basel, Basel, Switzerland

^d Institute of Pathology, University Hospital Basel, Basel, Switzerland

^e Department of Urology, Cantonal Hospital Baselland, Liestal, Switzerland

ARTICLE INFO

Article history:

Received 17 January 2016

Received in revised form

7 February 2016

Accepted 10 February 2016

Keywords:

Biomolecular and immunohistochemistry analysis

Renal cell carcinoma von Hippel-Lindau

Young adults

ABSTRACT

Renal cell carcinomas (RCC), mostly occurring in adults aged 60–70 years, can result from well-known factors like cigarette smoking, obesity and hypertension. However, they have been associated with genetic alterations in children and young adults. A 28 year-old male patient with a confirmed RCC underwent biomolecular and immunohistochemical analyses due to his young age. A point mutation of the von Hippel-Lindau tumor suppressor gene was identified. Young patients under 40 years with diagnosed RCC should undergo additional diagnostic investigation, hence the discovery of an underlying cause. This could be important for further treatment and counseling of these young patients.

© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Renal cell carcinomas (RCC) mostly occur in adults aged 60–70 years and are rare in children and young adults. They can result from well-known factors like cigarette smoking, obesity and hypertension in older patients and have been recently associated with genetic alterations in children and young adults.¹ We report and discuss our findings of a 28 year-old men in whom a RCC was diagnosed.

Case presentation

A 28 year-old Caucasian man with a renal mass in the intermediate ventral part close to the hilum of the right kidney underwent surgery without intraoperative or postoperative complications. Histological examination confirmed a 1.5 cm clear cell RCC (ccRCC, Fig. 1A) without infiltration of the renal capsule, i.e. TNM classification was pT1a, cN0, cM0, Fuhrman grade 2, R0.

Focused biomolecular and immunohistochemical analyses were performed to search for potential underlying genetic alterations.

Overexpression of transcription factor E3 (TFE3) (Fig. 1B) and transcription factor EB (TFEB) (Fig. 1C) for the translocation Xp11.2 as well as fluorescent in situ hybridization (FISH) tests for chromosomes 3 (3p11.1-q11.1), 7 (7p11.1-q11.1), 17 (17p11.1-q11.1), and deletion of chromosome 9 (9p21) were negative. Mutation analysis of the von Hippel-Lindau (VHL) tumor suppressor gene on chromosome 3 (3p25.3) revealed a point mutation of the Exon 1 (Fig. 2).

After more than 48 months, the patient had an uneventful follow-up without any relapse of the ccRCC. Furthermore, renal function was preserved with normal levels of serum creatinine and creatinine clearance.

Discussion

RCC is rare in patients under 40 years of age. Due to usage of ultrasound and computed tomography (CT), an increasing number of RCCs are discovered incidentally.¹ These RCCs are at presentation smaller and at lower stage.¹ Partial nephrectomy (PN) is the treatment of choice for localized T1a tumors over radical nephrectomy (RN) (grade of recommendation, GR: A; level of evidence, LE: 1b).¹

* Corresponding author. Department of Urology, Cantonal Hospital Aarau, Tellstrasse 25, 5001 Aarau, Switzerland. Tel.: +41 62 838 64 80; fax: +41 62 838 47 53. E-mail address: matthias.walter@ksa.ch (M. Walter).

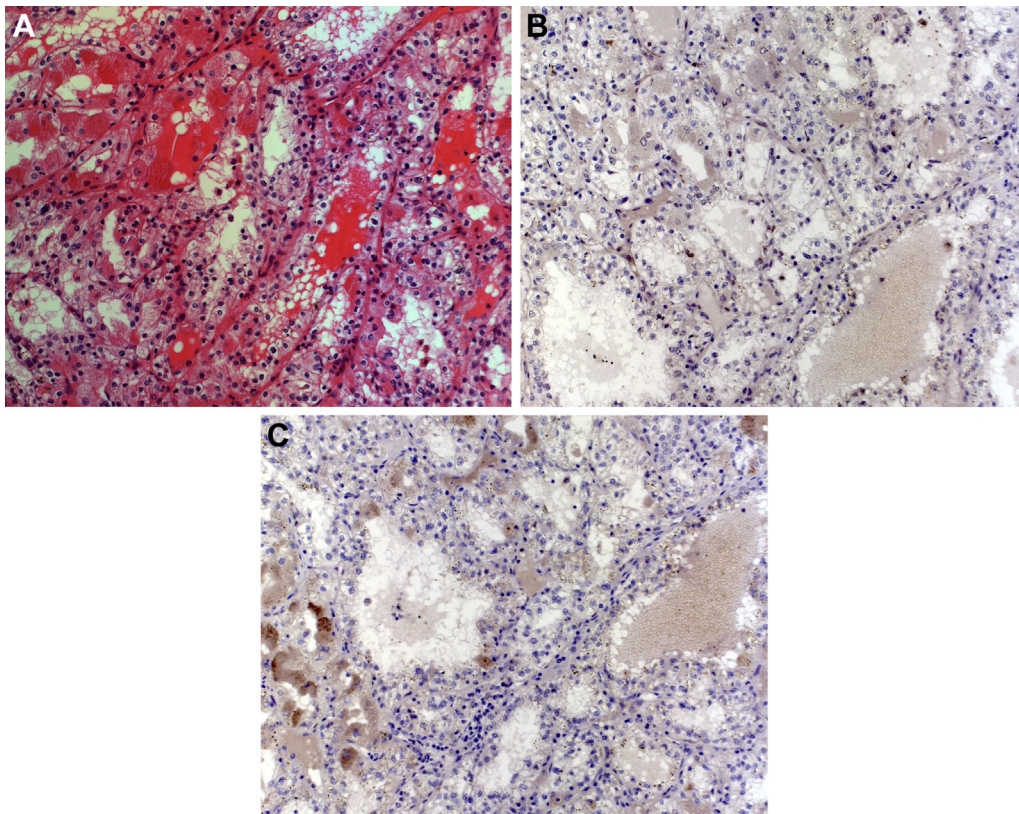


Figure 1. A: Hematoxylin and eosin (HE) stain: Clear cell renal cell carcinoma with tubular and solid aggregates of large tumor cells with ample clear cytoplasm, monomorphous vesicular nuclei and inconspicuous nucleoli (magnification $\times 20$). B: Negative immune-reactivity for transcription factor E3 (magnification $\times 20$). C: Negative immune-reactivity for transcription factor EB (magnification $\times 20$).

In this way, the patient underwent surgery to have his tumor removed. RCCs are most likely to occur in adults aged 60–70 years and mainly result from well-known etiological factors (LE: 2a) such as cigarette smoking, obesity and hypertension.¹ Presentation in children and young adults is rare and often associated with genetic alterations (e.g. VHL disease or Xp11.2 translocation).^{1,2} Therefore, additional diagnostic investigations on the renal specimens were carried out.

A point mutation of the VHL tumor suppressor gene on chromosome 3 (3p25.3) was detected upon further evaluation in this

patient, hence a “loss-of-function mutation.”^{1,3} De novo mutations are found in 20%, while VHL mutations are inherited in 80%.⁴ The autosomal dominant genetic disease usually presents with clinical manifestations within the second and fourth decade of life.³ In regard to RCC, the mean age is 39 years at presentation in patients with VHL disease, which is approximately 20 years earlier than for sporadic RCC.³ In addition to the young age of presentation, RCC associated with VHL disease also recurs more frequently.³

The VHL disease is also associated with other neoplasms such as pheochromocytoma, neuroendocrine tumor, pancreatic cyst, and endolymphatic sac tumor. Therefore, patients should undergo physical and radiologic investigations. In our patient no other suspicious lesion was detected and family history was inconspicuous.

To emphasize the importance of this matter, patients with VHL disease succumb early, i.e. median age of 49 years and a third of whom die from metastatic RCC.³

Therefore, patients should be counseled with regard to genetic analysis whether the VHL disease is present or not. Knowing whether one is carrying an underlying hereditary disease or not is crucial as it concerns not only patients, but also their children. It has been demonstrated that clinical screening of children at risk of VHL disease can detect tumors before the first symptoms become apparent and reduce morbidity consequently.⁵ Therefore, if a genetic alteration such as the VHL disease is missed, not only the life of this patient is in jeopardy but the prosperity of the entire family.

Our patient underwent regular, yet uneventful follow-up, as neither local recurrence nor metastatic progression occurred.

Unilateral recurrence rate and bilateral appearance of RCC are high in patients with VHL disease.³ Therefore, regular follow-up is warranted for each patient with VHL tumor suppressor gene

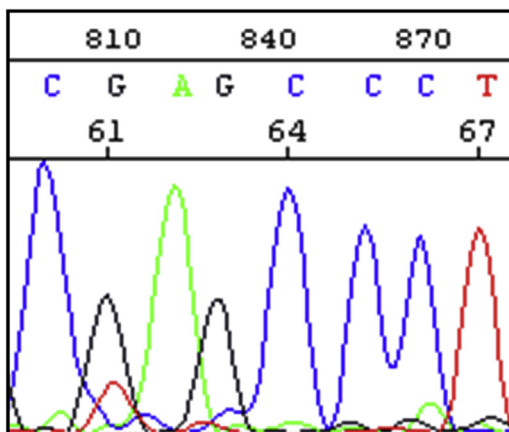


Figure 2. Gene sequence analysis: Red line indicating the point mutation (G to T) on nucleotide 810, resulting in a stop codon for transcription and loss of function of the von Hippel-Lindau tumor suppressor gene.

mutation to monitor tumor progression and to prevent transition into metastatic disease. Usually, patients are under close surveillance using imaging techniques such as CT or magnetic resonance imaging. In the unfortunate situation when metastases are detected, targeting agents, e.g. Sorafenib, should be considered for treatment, as neoangiogenesis resulting from an overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) is promoted by hypoxia-induced factor (HIF) accumulation in patients with VHL-Gene mutation.¹

Conclusion

Patients younger than 40 years of age with diagnosed RCC, additional diagnostic work up should be offered for exploration of potential underlying conditions such as VHL tumor suppressor gene mutation could be identified.

In case of an underlying condition such as the VHL disease, tailored treatment should be initiated to preserve renal function as long and as much as possible, and to limit cancer progression or relapse. Furthermore, patients at risk of carrying a hereditary disease must be informed and counseled accordingly.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A

copy of the written consent is available for review by the Editor of this journal.

Conflicts of interest

None of the contributing authors have any conflict of interest, including specific financial interest or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Acknowledgment

We would like to thank the patient for providing his data and history.

References

1. Ljungberg B, Bensalah K, Bex A, et al. *EAU Guidelines on Renal Cell Carcinoma*. 2015.
2. Audenet F, Yates DR, Cancel-Tassin G, et al. Genetic pathways involved in carcinogenesis of clear cell renal cell carcinoma: genomics towards personalized medicine. *BJU Int*. 2012;109(12):1864–1870.
3. Maestro MA, Martinez-Piñeiro L, Gonzalez ER. Renal tumors in patients with von Hippel-Lindau disease: "State of Art Review". In: Van Poppel H, ed. *Renal Cell Carcinoma*. InTech; 2011.
4. Maher ER, Neumann HP, Richard S. von Hippel-Lindau disease: a clinical and scientific review. *Eur J Hum Genet*. 2011;19(6):617–623.
5. Priesemann M, Davies KM, Perry LA, et al. Benefits of screening in von Hippel-Lindau disease – comparison of morbidity associated with initial tumours in affected parents and children. *Horm Res*. 2006;66(1):1–5.