

# Incidental Finding Of Renal Cell Carcinoma In Patients With Previous Choroidal Melanoma: Possible Genetic Linkage Through Defects In Chromosome 3

G Lamb, F Roberts, E Kemp, M Aitchison

## Citation

G Lamb, F Roberts, E Kemp, M Aitchison. *Incidental Finding Of Renal Cell Carcinoma In Patients With Previous Choroidal Melanoma: Possible Genetic Linkage Through Defects In Chromosome 3*. The Internet Journal of Urology. 2005 Volume 4 Number 1.

## Abstract

Renal cell cancer and choroidal melanoma are rare tumours. Defects in chromosome 3 are associated with sporadic lesions in both malignancies. To date no other cases of primary choroidal melanoma associated with incidental subsequent diagnosis of renal cell carcinoma have been published. We report the first two cases, both identified within a single institution within 3 years of each other. In addition we propose a causal link between both conditions due to common susceptibility of chromosome 3 to mutation.

## INTRODUCTION

Choroidal metastases from renal cell carcinoma primary are well documented (1). To our knowledge, there are only 2 previous reports of a choroidal melanoma associated with RCC (2,3). In both cases the RCC preceded the development of the choroidal melanoma. One patient had diffuse metastatic disease the other previously resected RCC. In both of our cases the renal cell carcinoma was discovered incidentally at routine surveillance scanning following treatment of choroidal melanoma.

Uveal melanoma is a rare tumour affecting 6-7 cases per million in North America (4). Similarly renal cell cancer incidence is reported as 6-12 cases per 100000 population (<http://www.cancerresearchuk.org>). Finding two patients with both independent, rare tumours, within the same institution raises the question of genetic predisposition to malignancy. We explore and discuss the possible mechanisms behind this association.

## CASE REPORT AND MANAGEMENT

### CASE REPORT 1

An 83 year old female presented to her general practitioner in 1999 with reduced visual acuity in her right eye. Ophthalmology referral was sought and a choroidal (also known as uveal) melanoma was diagnosed associated with a detached retina of the eye. Choroidal melanoma is a clinical

diagnosis, treated on suspicion and observation (5).

Accordingly she was treated by temporary insertion of ruthenium plaque brachytherapy rather than enucleation. No formal tissue diagnosis was established. Complete response was observed with no local recurrence at follow up.

At routine follow up CT scanning 17 months following initial diagnosis a 5cm upper pole lesion was identified incidentally in the left kidney. In view of the suspicion of metastatic melanoma CT guided biopsy was performed which confirmed a low-grade neoplasm of renal origin.

In view of the patient's general frailty and age, along with the low grade, the patient was treated conservatively and died of unrelated illness with no evidence of metastases or increase in tumour size 33 months after diagnosis of her renal lesion.

### CASE REPORT 2

A 72 year old female presented in 2002 with reduced visual acuity in her right eye associated with floaters. At ophthalmology review a peripheral lesion in the right temporal region was identified and thought to represent a choroidal melanoma. To confirm this diagnosis serial ultrasound scanning was performed which demonstrated the lesion to increase in size over the following month.

The patient proceeded to treatment by temporary ruthenium plaque insertion, with a complete local response. Routine

surveillance ultrasound scanning of the liver identified textural changes of the liver parenchyma and CT scanning was carried out. This identified a 2cm possible cyst or mass at the lower pole of the right kidney as an incidental finding, the liver was normal. MRI confirmed the lesion was solid rather than cystic 4 months after initial presentation.

In view of the possibility of metastatic melanoma CT guided biopsy was performed, the initial biopsy inconclusive with repeat biopsy confirming renal cell carcinoma.

The patient recently underwent partial nephrectomy which confirmed the presence of clear cell carcinoma with chromophil elements. She remains alive and well 34 months after surgery with no evidence of metastatic disease from either primary.

## **DISCUSSION**

The von Hippel-Lindau (VHL) tumour suppressor gene has been mapped, using genetic linkage studies, to the short arm of chromosome 3 at 3p25-26 (6). Defects in this gene result in von Hippel-Lindau disease, an autosomal dominant condition characterised by highly vascular tumours of multiple organs, including the CNS, kidney, adrenal and pancreas. There is a 70% probability of these patients developing renal cell carcinoma (RCC) by the seventh decade (7).

Fifty to sixty-five percent of non-familial sporadic clear cell RCCs demonstrate mutations of the VHL gene (8). 85% of these tumours demonstrate loss of heterozygosity at the VHL locus.

Uveal melanoma is a rare tumour but represents the most common primary intraocular malignancy in adults (3). Cytogenetic investigations of cultured uveal melanoma cells have revealed the majority of choroidal and ciliary body melanomas are characterised by non-random alterations in chromosomes 3, 6 and 8 (9).

Further studies by Parrella et al demonstrate the highest incidence of loss of heterozygosity to be found on chromosome 3 accounting for 64% of cases (10). In their study 59% showed allelic loss of all informative markers on chromosome 3, consistent with monosomy 3 (M3). The loss of chromosome 3 is a highly specific marker for poor prognosis in choroidal melanoma (11).

Finding two patients with both independent tumours suggests an inherent propensity to mutation of chromosome

3 during cell division in these cases, although the mechanism is unclear.

Tumours as a result of defects at the VHL gene are thought to arise according to the Knudson two hit model for tumour suppressor genes (12). The loss of heterozygosity, or allelic loss of chromosome 3 previously demonstrated in patients with uveal melanoma may represent a susceptibility to a "second hit". Any mutation or heterozygosity at the VHL locus (first hit) would be expressed in the event of M3 allelic loss of the functioning VHL gene.

Primary choroidal melanoma associated with subsequent diagnosis of renal cell carcinoma has not been previously reported. We propose a causal link between both conditions due to common susceptibility of chromosome 3 to mutation.

The two cases, both identified within a single institution within 3 years of each other, represent the first to be published in the literature.

## **ACKNOWLEDGEMENT**

The authors gratefully acknowledge the funding provided by the "Fischer Foundation", a charitable organisation dedicated to research in renal cancer.

## **CORRESPONDENCE TO**

Gavin W. A. Lamb Department Of Urology C/O Mr Aitchison's secretary Gartnavel General Hospital 1053 Great Western Rd Glasgow G12 0YN, UK e-mail: glam@doctors.org.uk Tel: 44 (0)141 211 0128

## **References**

1. Haimovici R, Gragoudas ES, Gregor Z, Pesavento RD, Mieler WF, Duker JS. Choroidal metastases from renal cell carcinoma. *Ophthalmology*. 1997; 104(7): 1152-1158
2. Kremer I, Gabbay M, Yassur Y. Choroidal melanoma with massive lipid exudation in a patient with metastatic hypernephroma. *Annals of Ophth*. 1992; 24(3): 93-96.
3. Lureau MA, D'Hermies F, Mashhour B, Morel X, Validire P, Renard G. Choroidal melanoma associated with 2 other primary malignant lesions. *J Fran. D Opth*. 1998; 21(2): 128-132.
4. Scotto J, Fraumeni JF, Lee JAH. Melanomas of the eye and other noncutaneous sites: epidemiologic aspects. *J Natl Cancer Inst*. 1976; 56: 489-91.
5. DePotter P, Shields CL, Shields JA. New treatment modalities for uveal melanoma. *Curr Opin Ophth* 1996; 7;111: 27-32.
6. Latif F, Tory K, Gnarr J et al. Identification of von Hippel-Lindau disease tumour suppressor gene. *Science* 1993; 260: 1317-20.
7. Maher ER, Kaelin Jr WG. Von Hippel-Lindau disease. *Medicine* 1997; 76: 381-91.
8. Gnarr JR, Tory K, Weng Y et al. Mutations of the VHL tumour suppressor gene in renal carcinoma. *Nat Genet* 1994;

***Incidental Finding Of Renal Cell Carcinoma In Patients With Previous Choroidal Melanoma: Possible Genetic Linkage Through Defects In Chromosome 3***

---

7: 85-90.

9. Becher R, Korn WM, Prescher G. Use of fluorescent in situ hybridisation and comparative genomic hybridisation in the cytogenetic analysis of testicular germ cell tumours and uveal melanomas. *Cancer Genet. Cytogenet.* 1997; 93: 22-8.

10. Parrella P, Sidransky D, Merbs SL. Allelotype of posterior uveal melanoma: Implications for a bifurcated

tumour progression pathway. *Canc Res.* 1999; 59: 3032-37.

11. Prescher G, Bornfeld N, Hirche H, Horsthemke B, Jockel KH, Becher R. Prognostic implications of monosomy 3 in uveal melanoma. *Lancet.* 1996; 347: 1222-1225

12. Knudson AG. VHL gene mutation and clear-cell renal carcinoma. *Cancer J Sci Am.* 1995; 1: 180.

**Author Information**

**Gavin W.A. Lamb**

Department Of Urology, Gartnavel General Hospital

**Fiona Roberts**

Department Of Pathology, Western Infirmary

**Ewan G. Kemp**

Department of Ophthalmology, Gartnavel General Hospital

**Michael Aitchison**

Department Of Urology, Gartnavel General Hospital