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

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Citation

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 (9).
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 (9). 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 (10).

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.

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