Renal cell carcinoma in a von Hippel-Lindau syndrome: when should phaeochromocytoma be anticipated?

Azarisman S M S, Nor Azmi K

ABSTRACT

A 39-year-old man was diagnosed with von Hippel-Lindau syndrome, which was associated with retinal haemangioblastoma, cervical cord haemangioblastoma and bilateral renal cell carcinoma. He subsequently underwent an arterial embolisation and cervical laminectomy, following a spinal angiogram of the cervical lesion. He also had a right radical nephrectomy, with no perioperative complications. However, on admission for the left radical nephrectomy, he was noted to have preoperative hypertension. Further investigation revealed an enlarged left adrenal gland on abdominal computed tomography scan and raised urinary catecholamines. We discuss the risk of renal cell carcinoma and phaeochromocytoma arising concomitantly in von Hippel-Lindau syndrome, and how best to investigate and manage them.

Keywords: phaeochromocytoma, renal cell carcinoma, von Hippel-Lindau Syndrome

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INTRODUCTION

Von Hippel-Lindau syndrome (vHL) is an autosomal, dominant, inherited familial cancer syndrome, which comprises retinal and central nervous system haemangioblastomas, cysts or tumours of the kidneys, adrenal glands, pancreas, epididymis and endolymphatic sacs.[1] It may be subdivided into several groups, in which either renal cell carcinoma (RCC) or phaeochromocytoma predominates. However, both may be present concurrently.

Genetic studies of families with vHL syndrome have identified the types of mutation that lead to the development of RCC and phaeochromocytoma. This has enabled clinicians to reliably predict the presence of either condition, prior to presentation, and initiate treatment based on the underlying genetic abnormalities. Furthermore, families of patients with vHL can be counselled on their risk of developing vHL based on genetic studies.

This report illustrates the case of a RCC-predominant vHL, which was noted to have features suggestive of phaeochromocytoma preoperatively, and which was subsequently confirmed biochemically and radiologically. We discuss the risk of RCC and phaeochromocytoma arising concomitantly with vHL syndrome, and the underlying genetic abnormality associated with it.

CASE REPORT

A 39-year-old man, who presented initially in November 2002 to a private institution, complained of a nine-month history of progressive weakness and numbness of both upper and lower limbs, predominantly on the right, associated with difficulty in passing urine. Physical examination revealed signs of spastic tetraparesis with a sensory level at the fourth cervical dermatome (C4). Magnetic resonance (MR) imaging of the spine showed an intramedullary cord tumour with associated syringomyelia at the fourth and fifth cervical vertebra (C4–C5) level, consistent with an intramedullary haemangioblastoma (Fig. 1).

A preoperative angiographic embolisation of the spinal cord tumour was performed, followed by excision and laminoplasty (Fig. 2). During his preoperative work-up, he was noted to have a retinal lesion on fundoscopy and ballotable abdominal masses. These were later confirmed to be a right retinal haemangioblastoma and bilateral polycystic kidneys on abdominal computed tomography (CT). A 1 cm diameter hypodense adenoma in the left adrenal gland, which enhanced homogeneously, was also seen (Fig. 3a). The patient's blood pressure and renal function remained normal throughout this period. Preoperatively, the patient did not have any history to suggest phaeochromocytoma. His father died at the age of 36 years of a 'brain tumour', and an elder brother who is only 40 years of age has hypertension. Several of his uncles died of unknown causes at relatively young ages, but he was not privy to any details pertaining to these deaths.

Department of Internal Medicine, Faculty of Medicine, International Islamic University Malaysia, Jalan Hospital Campus, Kuantan 25150, Malaysia

Azarisman SMS, MBBS, MMed
Assistant Professor

Department of Medicine, Hospital Universiti Kebangsaan Malaysia, Jalan Tenteram, Bandar Tun Razak, Kuala Lumpur 56000, Malaysia

Nor Azmi K, MBBS, MMed
Senior Consultant Endocrinologist and Head

Correspondence to:
Dr Azarisman Shah Mohd Shah
Tel: (60) 9 513 2797 ext 3449
Fax: (60) 9 513 3615
Email: risman1973@hotmail.com

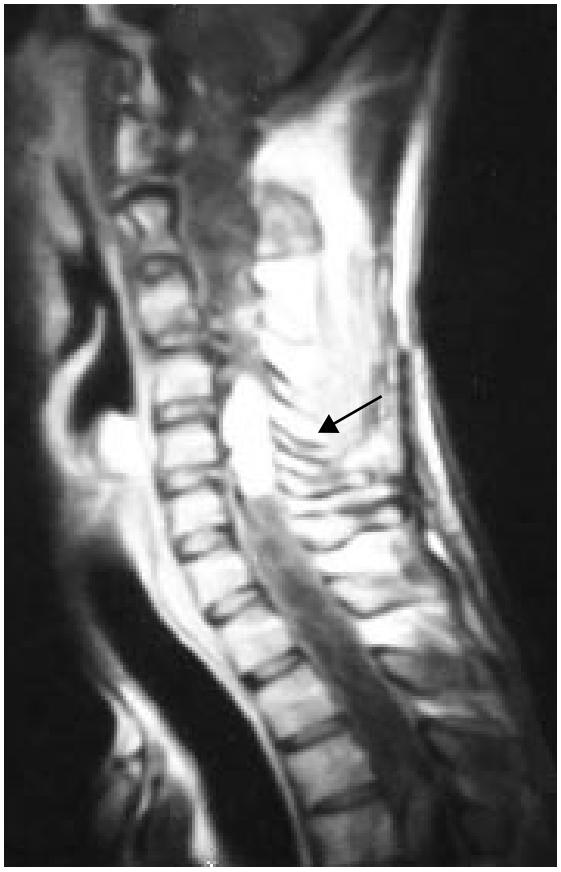
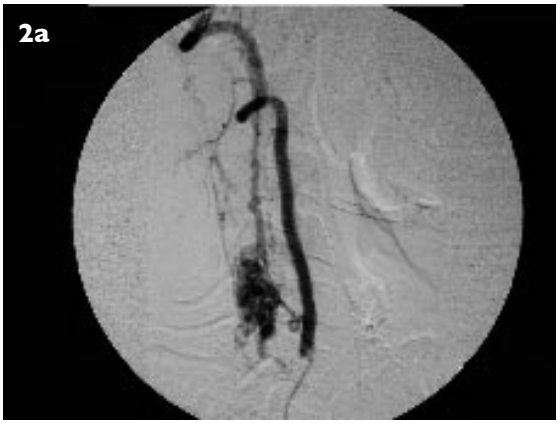


Fig. 1 Enhanced sagittal T1-W MR image of the spine shows an intramedullary haemangioblastoma at the C4–C5 region (arrow).



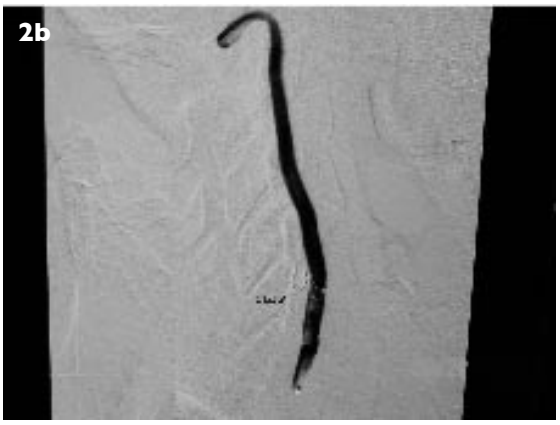
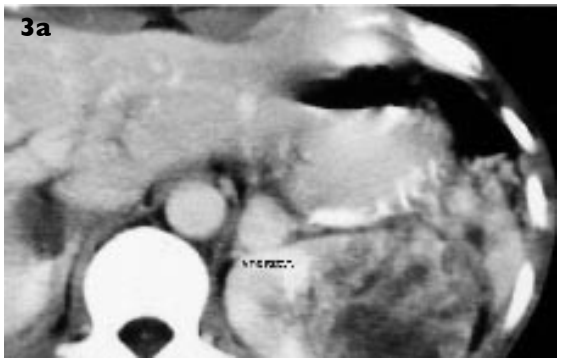


Fig. 2 (a) Preoperative angiogram shows hypervascularity of the intramedullary tumour; (b) Post-embolisation angiogram shows marked reduction of tumour vascularity.



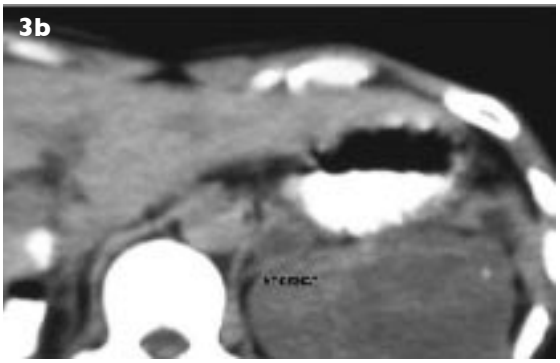


Fig. 3 Abdominal CT images show (a) an enlarged left adrenal gland; and (b) one year later, a larger adrenal gland with a cystic component.

It was decided that the risk of underlying RCC was sufficient to warrant bilateral radical nephrectomies, due to the presence of solid enhancing components to the cysts. He was counselled for bilateral nephrectomies and the need to undergo renal replacement therapy ad infinitum postoperatively. In July 2003, he underwent a right radical nephrectomy, which confirmed the presence of clear-cell RCC on histopathological examination. The resected right adrenal gland was normal, and during the perioperative period, his blood pressure again remained within the normal range. The patient remained under follow-up, but initially refused to proceed with the left radical nephrectomy due to monetary constraints. He subsequently agreed to proceed in June 2004, and during the interval period, his blood pressure remained normal and he denied any symptoms associated with phaeochromocytoma.

However, when admitted for the left radical nephrectomy in June 2004, he was noted to be hypertensive. A repeat CT showed that the left adrenal gland had increased in size and was associated with central hypodensity, representing a cystic component typical of phaeochromocytoma (Fig. 3b). 24-hour urinary catecholamines also revealed a two-fold increase in the urinary noradrenaline excretion. With the diagnosis of concurrent phaeochromocytoma, he was started on an alpha-antagonist and intravascular volume repletion preoperatively. The patient, however, refused further surgery and discharged himself.

DISCUSSION

vHL syndrome has an estimated prevalence of 2–3 per 100,000 population, worldwide.[2] Although highly variable, tumours typically develop in patients with vHL in the second to fourth decades of life.[3] Phaeochromocytoma occurs in 10%–20% of patients with vHL, whereas RCC occurs in one-third of these patients.[1] Morbidity and mortality from vHL can be reduced by the identification and surveillance of affected individuals and at-risk relatives at an early presymptomatic stage.[1]

As is true for most hereditary cancer syndromes, vHL is linked to inactivation of a tumour suppressor gene.[3] This gene is located on the chromosome 3p25-p26, and depending on the type of genetic abnormality present at this gene, is highly correlated with the vHL subtype, which manifests phenotypically.[1] vHL can be subdivided into type 1 (low risk of phaeochromocytoma) and type 2 (high risk of phaeochromocytoma). Type 1 disease is associated with large deletions and mutations resulting in a truncated vHL protein, thereby conferring a lower risk for phaeochromocytoma.[1] Type 2 is subdivided into type 2A (low risk of RCC), type 2B (high risk of RCC) and type 2C (phaeochromocytoma only). Type 2 disease is almost invariably associated with vHL missense mutations, suggesting that phaeochromocytoma reflects a vHL "gain of function" or that complete loss of vHL protein function is incompatible with the development of phaeochromocytoma.[3] These germline mutations are the subject for DNA surveillance of patients and their families.

The phenotypic presentation of bilateral clear-cell RCC in this patient suggests that he is of vHL type 1 or type 2B. Although RCC is usually attributed to a "loss of function" and phaeochromocytoma to a "gain in function" resulting from the underlying genetic abnormality, exceptions do occur. Furthermore, the presence of both RCC and phaeochromocytoma can be seen in vHL types 2A and 2B, in which their concurrent presence cannot be explained merely by the "loss or gain of function", mutations as described in vHL types 1 and 2C.

Phaeochromocytoma associated with vHL represents a distinct entity separate from that of sporadic phaeochromocytoma. They represent about 10% of the total and tend to be multifocal and recurrent. Up to 35% of these patients are asymptomatic with normal blood pressure and urinary catecholamines.[1] Clinically-silent phaeochromocytoma tend to manifest itself intraoperatively, as a result of the release of catecholamines triggered by anaesthesia induction and also intubation.[4]

In this particular case, the initial abdominal CT finding of adrenal adenoma should have been followed up with at least a biochemical evaluation for hormone excess in accordance with the National Institutes of Health consensus on adrenal incidentalomas.[5] The investigative modality of choice would have been plasma noradrenaline and normetanephrine, as they have been proven to be highly sensitive and specific for phaeochromocytoma arising from vHL.[6]

The reason that further investigation was not pursued was because the patient was completely asymptomatic; the blood pressure was normal, there was no intraoperative complications during the cervical laminectomy, and the adenoma was small (less than 3 cm) and may have constituted a benign or non-functioning incidentaloma.[5] Had urinary and plasma catecholamines or metanephrines been tested at the time, they could have been negative due to the size of the tumour at that stage.

The presence of phaeochromocytoma in this patient was later confirmed with a two-fold increase in urinary noradrenaline, which has a diagnostic sensitivity and specificity close to 100% and 95%, respectively,[1] along with an enlarged adrenal gland with a cystic component on the abdominal CT. The concurrent presence of phaeochromocytoma and RCC seems to suggest an underlying classification of vHL type 2B, which can only be confirmed via genetic examination.

In conclusion, vHL syndrome is a rare genetic disorder, which results in the formation of multiple blood vessel tumours and visceral cysts or tumours.[3] Depending on the underlying genetic defect, it could predispose to the formation of either RCC or phaeochromocytoma. However, these are not mutually exclusive, and the concurrent presence of both entities is well-documented and the underlying genetic abnormality has been well characterised.

Patients with RCC-predominant vHL should therefore be investigated for concurrent phaeochromocytoma, especially when they are planned for surgery. The investigative modality should include

urinary and plasma noradrenaline or normetanephrines due to their high level of sensitivity and specificity. Even if the initial findings are inconclusive, they should nevertheless be conditioned for phaeochromocytoma preoperatively, as the risk of a silent phaeochromocytoma manifesting itself intraoperatively is significant enough to warrant erring on the side of caution.

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