CASE REPORT

A Rare Case of Von Hippel Lindau Disease

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Summary

Pheochromocytoma is a rare catecholamine-secreting tumour typically arising within the adrenal medulla [1]. It may occur sporadically or be associated as part of a tumour syndrome including Von Hippel Lindau (VHL), Multiple Endocrine Neoplasia (MEN) 2 and Neurofibromatosis Type 1. VHL is associated with multi-organ involvement of benign and malignant tumours characterized by the presence of retinal angiomas, hemangioblastomas of the cerebellum and spinal cord, renal cell carcinomas, pheochromocytomas and other cystic lesions in the kidneys, pancreas, and epididymis. It is a rare disorder with prevalence estimated at 2-3 per 100,000. This case report describes a 37 years old Chinese gentleman who presented to our institution for further management of bilateral pheochromocytoma and retinal angioblastoma with problems of duodenal ulcer and anaemia. There was no family history of similar problems. With these features the criteria for the diagnosis of von Hippel Lindau disease was established [2].

Key Words: Pheochromocytoma, Optic disc angioma, Von Hippel Lindau Disease, Adrenalectomy, Renal cell carcinoma, Cerebellar hemangioblastoma.

Case Report

A 37 year old, Chinese gentleman, who had been residing in Japan for the past ten years, was referred to our institution for further management of pheochromocytoma with bilateral adrenal mass.

His initial complaints were mainly epigastric pain for many years associated with belching. He came back to Malaysia about one month prior to his admission with worsening symptoms of anaemia, mainly lethargy and loss of appetite. There was no malena. He was an ex-intravenous drug abuser with needle sharing ten years previously and sexual promiscuity. He smoked 40 cigarettes per day, had alcohol occasionally and he did not keep pets. He had a divergent squint of the right eye, which he contributed to a motor vehicle accident in Japan about five years ago. This was associated with loss of visual acuity to the degree of perception of movements only.

On examination he was of medium build. There was mild pallor, but he was not jaundiced. There was no flushing or tremor. There was evidence of finger clubbing and presence of spider nevi but there was no Dupuytren's contracture or onycholysis. There was no goiter. His vital signs were stable with blood pressure of 130/80 mmHg (sitting) and 130/90 mmHg (standing). The pulse rate was 100 beats per minute of regular rhythm. On examination of the precordium there was a systolic murmur at the left sternal edge of grade 3/6. His lungs were clear. On light palpation of the abdomen there was no obvious mass and there was no organomegaly. He had a divergent squint of the right eye. Fundoscopy of the same eye showed abnormal finding of possible optic atrophy. Otherwise there was no other neurological manifestation.

He was initially admitted to a private institution where he was noted to have microcytic, hypochromic anaemic with Hb of 7.7 g/dL. The white cell count was within

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normal range with thrombocytosis of 827 x 10^9/L. His renal, liver and lipid profiles were normal and he was not hyperglycemic. His ESR level was raised to 70 mm/hr. Calcium and phosphate levels were within normal limits. His thyroid function tests were normal. Retroviral screening was negative. An oesophagogastroduodenoscopy (OGDS) showed a non-bleeding duodenal ulcer at D1 level. His blood pressure was persistently high at 160/110 mmHg. He was started on oral Amlodipine 10 mg daily and Prazosin 1 mg tds. A routine chest radiograph showed multiple nodular shadowing in both lung fields supported by a CT scan of the thorax, which revealed multiple well circumscribed nodules with no evidence of lymph node involvement. A CT scan of the abdomen showed bilateral adrenal mass, the left adrenal measuring 8 x 10 x 9.5 cm dimensions. See Fig 1.

The 24 hour urine collection for catecholamines showed an adequate urine sample with markedly elevated Noradrenaline secretion of 19,967 nmol (Normal range(NR) : 40-780 nmol). The other catecholamines were slightly elevated with Adrenaline of 153 nmol (NR : 5-80 nmol) and Dopamine of 5,470 nmol (NR : 200-3500nmol).

Echocardiogram done was normal. He was then referred to our institution for surgery. He had an ophthalmic consult, which showed evidence of optic disc angioma of the right eye, which probably explained his loss of vision. See Fig 2.

The presence of pheochromocytoma with the background problem of this vascular tumour raises the possibility of von Hippel Lindau syndrome. An MRI of the brain did not reveal any cerebellar haemangiomas. There was no renal cell carcinoma or other visceral cysts on the abdominal CT scan examination. The presence of the multiple lung nodules and the duodenal ulcer suggested haemangiomas at those atypical sites or possibility of malignant pheochromocytomas metastasized to the lungs.

He was adequately hydrated and his antihypertensive agents were optimized to include Prazosin 3mg tds, Labetolol 400mg qid and Nifedipine 20mg tds. Oral Phenoxybenzamine was not available at the time of his admission.

He underwent a laporoscopic bilateral adrenalectomy, which was complicated by a transient hypotensive episode following ligation of the right adrenal vein. The pheochromocytoma is confirmed by tissue histopathological examination which showed sheets of large, closely packed polyhedral cells in well-defined nests bound by delicate fibrovascular stroma. There were no features to suggest malignant cells. A CT guided biopsy of the multiple lung nodules, done a month later was indeterminate as it only showed collapsed alveoli and bronchial tissue with no evidence of malignancy.

He recovered well with good blood pressure control with only Atenolol 100mg daily. He is currently awaiting genetic profiling for VHL disease.

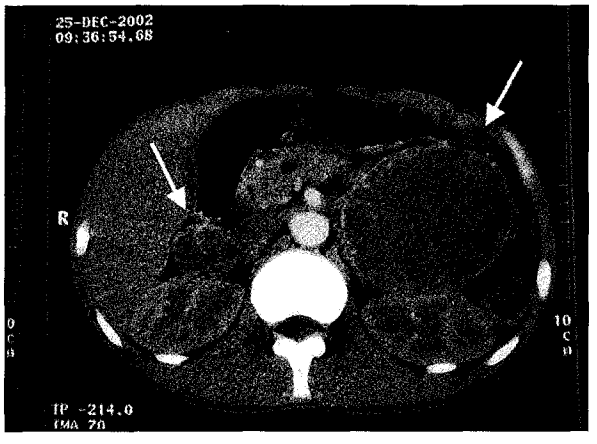

Fig 1: CT scan of the abdomen showing bilateral extra-adrenal masses

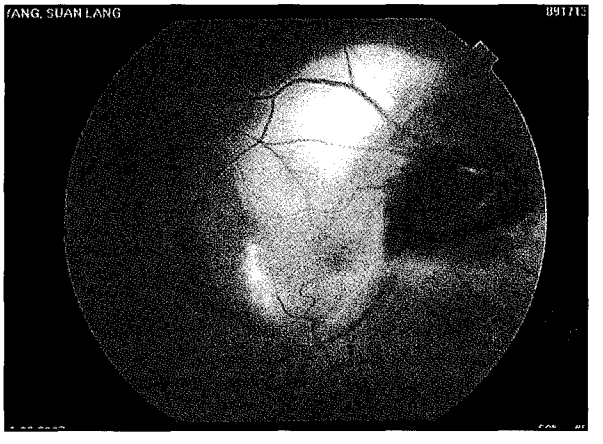

Fig 2: Fundoscopy showing optic disc angioma of the right eye

Discussion

Von Hippel Lindau (VHL) disease is an autosomal dominant inherited tumor syndrome, characterized by benign and malignant tumors in multiple organ systems, predominantly abundant vascularized tumors including retinal angioma and other haemangioblastoma in the cerebellum and spine; renal cell carcinoma; pheochromocytoma; islet cell tumors of the pancreas and endolymphatic sac tumors[1]. There is no single unique pathognomonic finding. Other features may be present including angiomatous or cystic lesions in the kidneys, pancreas, and epididymis.

The disease has an estimated prevalence of 2-3 per 100,000 persons with geographical variations[1]. It is seen in all ethnic groups with equal numbers in both sexes. The age at diagnosis varies from infancy to the seventh decade of life or later.

The main concern with our patient was pheochromocytoma, which is a tumour of chromaffin cells, presenting typically within the adrenal glands, and characterized by excess production of catecholamines. This was suspected in him with the presentation of hypertension at a relatively young age. Approximately 20% of all pheochromocytomas are due to VHL[2]. Pheochromocytoma may present in other tumour syndromes including Multiple Endocrine neoplasia Type 2 and Neurofibromatosis Type 1. Pheochromocytomas seen in VHL differ from those in sporadic cases as they are diagnosed in younger age group and are often bilateral, multiple, and extra-adrenal with infrequent metastases. Therefore in our patient the lung nodules raised the possibility of pulmonary angioma, which was fortunately excluded.

With negative family history, our patient was initially thought to be a sporadic case of pheochromocytoma. However, with a single hemangioblastoma with a characteristic visceral tumour of pheochromocytoma or renal cell carcinoma, the diagnosis of VHL can be made. With a positive family history, the presence of at least one typical VHL tumor should suffice[1].

Clinical diagnosis of VHL disease can be confirmed by DNA analysis, which shows a chromosomal abnormality of the VHL gene, at 3p25-26[3]. This germline VHL mutation have been detected in almost 500 families with VHL. VHL disease is divided into four clinical subtypes with interfamilial and intrafamilial variability and there is no simple relationship between a genotype and the manifestation of VHL-related tumors [1].

Pheochromocytoma in VHL may be asymptomatic or may manifest as the only symptom, as in our patient and findings on biochemical tests and MRI may be unremarkable[2]. It is unpredictable, and previously inactive pheochromocytomas may suddenly become life threatening especially intraoperatively. This can be especially risky if an unsuspected pheochromocytoma is present in a patient with VHL who has a cerebellar hemangioblastoma or if the patient is undergoing surgery for any of the other associated lesions. Screening for pheochromocytomas before surgery consists of 24-hour urinary metanephrine and catecholamine determinations. Pheochromocytoma from VHL patients had been shown to consistently display noradrenergic type of catecholamine in contrast to the expression of adrenergic type in MEN 2. Our patient had two subsequent sets of 24 hours urine catecholamines to demonstrate the reduction in the levels of catecholamines before surgery. He also had numerous 24 hours ambulatory BP monitoring to ensure that adequate BP control was achieved preoperatively to avoid sudden elevation in circulating catecholamines during manipulation leading to hypertension and arrhythmia during surgery.

Retinal angiomas (hemangioblastomas), which are benign tumours, are more commonly associated with VHL. Present in more than half of VHL patients, they are often multiple, bilateral, and recurrent. Our patient had initially associated his loss of vision in the affected eye to a motor vehicle accident that occurred earlier. On further history this condition had a delayed course. Patients with retinal angioblastoma in VHL are often asymptomatic until if untreated, serious damage may occur due to hemorrhage, retinal detachment, or other complications leading to blindness.

Because of the advances in medical facilities, metastases from clear cell renal carcinoma had become the most common cause of death followed by previously notorious neurological complications from cerebellar hemangioblastoma[1]. When VHL is diagnosed in a patient, lifelong and close follow-up for multiple and recurrent tumors is necessary with annual ultrasonograph or CT examination or both. The diagnosis of VHL also has implications for family members of the patient, potentially involving many relatives. If chromosomal analysis of the affected patient results in an identifiable mutation, at-risk relatives can be offered the option of presymptomatic gene testing.

References

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