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CASE REPORT

CEREBELLAR HEMANGIOBLASTOMA IN A PATIENT WITH VON HIPPEL-LINDAU DISEASE : A CASE REPORT

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A 23 year-old Chinese woman presented with symptoms of increased intracranial pressure due to obstructive hydrocephalus as a sequel to a mass effect from cerebellar haemangioblastoma. She underwent removal of the right cerebellar haemangioblastoma and ventriculo-peritoneal shunting. She also had bilateral retinal haemangioblastoma, left renal carcinoma, renal and pancreatic cysts without phaeochromocytoma. A left partial nephrectomy was performed for renal cell carcinoma followed by radiotherapy. She survived the initial episode only to succumb to another cerebellar haemorrhage 18 months later.

Key words : *Cerebellar hemangioblastoma, von Hippel-Lindau Disease*

Case Report

A 23 year-old Chinese woman without any family history of von Hippel-Lindau disease (VHL) presented with headache, diminishing vision and a few episodes of generalized fits for one year. Physical examination revealed right 6th and left 8th cranial nerves palsies. Funduscopy showed bilateral papilloedema with bilateral haemangiomata. The visual acuity in both eyes was 6/24. Cerebellar functions were intact. Blood investigation revealed a haemoglobin level of 12.2 gm/dl with red blood cell count of 5.08 million/mm^3. A computed tomographic scan of the brain showed a well defined rim enhancing right cerebellar cystic lesion with a heterogenous enhancing intramural nodule within, compressing the 4th ventricle with obstructive hydrocephalus (figure 1). Computed tomographic scan of abdomen showed multiple cystic lesions in both kidneys and pancreas with a lesion suspicious of carcinoma at the upper pole of the left kidney (figure 2). Urine VMA was negative.

Emergency external ventricular drainage was done on admission. This was followed immediately by a sub occipital craniectomy and resection of the tumour. A 3x3x2 cm solid nidus involving the right cerebellar hemisphere was noted. A ventriculoperitoneal shunt was performed as a second procedure. She was than referred to the nephrologist for the management of the left renal tumour. Histopathological examination (HPE) (figure 5) showed anastomosing network of capillary vessels interspersed with nests of stromal cells with moderate amount of pale pink cytoplasm. However, no mitosis was noted. On immunohistochemistry, the stromal cells were focally positive for vimentine, S 100 protein and neuron specific enolase (NSE) and negative for factor VIII related antigen (F VIII R Ag), glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA) and cytokeratin (CK).

Further investigation by angiography showed tumor blushes in other areas of the cerebellum suggesting multiple haemangioblastomas (Figures 2 and 3). These lesions were confirmed on MRI, which showed multiple enhancing nodules in the left cerebellar hemisphere (figure 4). The patient however died 18 months later due to a second cerebellar haemorrhage.

Discussion

VHL is a rare disease that has been recognised

for about 70 years. Eugene Von Hippel, an ophthalmologist described hereditary haemangioblastoma involving the retina in 1904. In 1926 Arvil Lindau, also an ophthalmologist recognized the association between retinal, cerebellar and visceral haemangioblastomas. The syndrome was later termed von Hippel-Lindau disease by Van der Hoeve. The criteria for diagnosis of VHL disease is given in table 1.

VHL demonstrates an autosomal dominant pattern of inheritance; a parent who carries the VHL gene will have offspring with a 50% chance of also having the VHL gene. Some families have fewer than 50% affected offspring and some parents of affected offspring do not manifest VHL even though they are "obligate carriers". This is due to incomplete penetrance where the gene is inherited but not expressed. It appears many of these cases are asymptomatic carriers. One to three percent of VHL cases arise without a family history, probably due to a new mutation. (3-4).

The study of various tumors from patients with VHL revealed loss of the 25-26 locus of the short arm of chromosome 3 (3p25-26) (3-5). (4) These genes are recognized as "VHL gene". A segment of DNA within the 3p25-26 locus is consistently transmitted with the disease and is used clinically to identify asymptomatic family members (5). Currently the precise mutations within the gene are being defined but there may be a "fragile" site within the gene associated with a particular tumor, such as renal cell carcinoma.

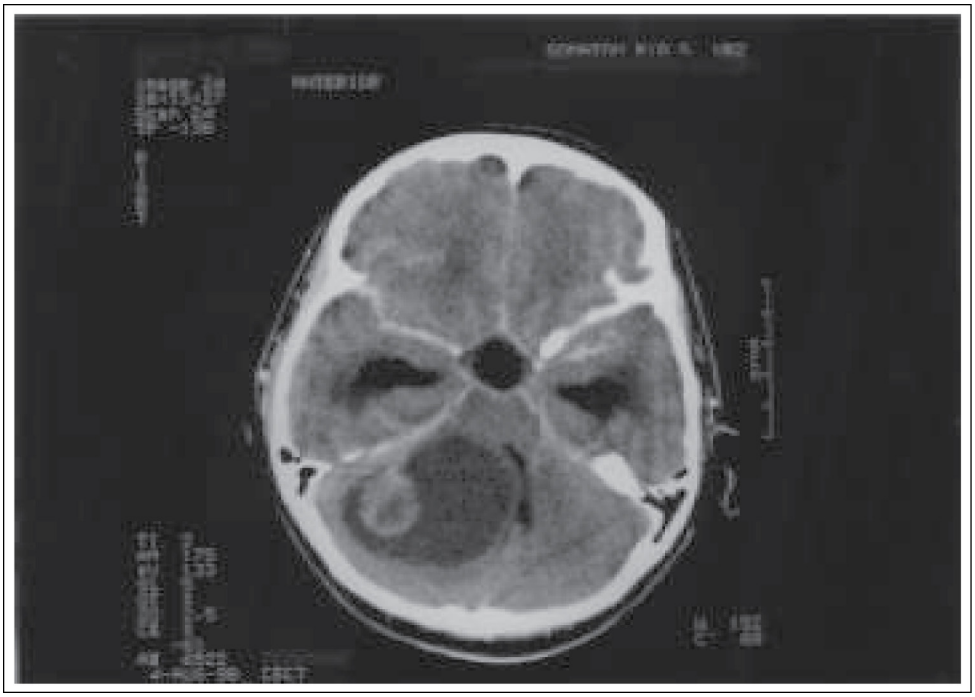
Table 1: Diagnostic features of von Hippel-Lindau Disease.

Ocular	Retinal haemangioblastoma
Visceral	Multicystic renal disease
	Renal cell carcinoma
	Phaeochromocytoma
	Pancreatic cysts
	Epididymal cysts
Central nervous system	Cerebellar haemangioblastoma Haemangioblastoma of other CNS location (cortex, spinal cord, brain stem)

The prevalence of VHL has been estimated to be between 1:35,000-1:53,000 (6-7) and there will be an estimated 500 VHL patients in Malaysia. In Hospital Universiti Sains Malaysia 15 cases have been reported since 1985. With modern and sensitive imaging modalities such as magnetic resonance imaging, more cases will be detected.

The average duration of symptoms of cerebellar haemangioblastoma before diagnosis is about one year. Occipital headache and cerebellar signs are seen in 75% of patients. Specific cerebellar signs vary with the location of the tumour. Midline

Figure 1: Axial CT scan of the brain with contrast showing a well defined rim enhancing cystic lesion with heterogeneously enhanced mural nodule compressing the 4th ventricle resulting in obstructive hydrocephalus.



tumour causes truncal ataxia, whereas dysmetria is more common in patients with laterally situated tumour. Symptoms of increased intracranial pressure result from obstructive hydrocephalus. Specific cranial neuropathies reflect brain stem involvement.

The mean ages (and ranges) of diagnosis of retinal, cerebellar haemangioblastoma and renal cell carcinoma are 25 years (1-67 years), 30 years (11-78 years) and 37 years (16-67 years) respectively. Families with phaeochromocytoma as a principal feature of the disease often develop phaeochromocytoma before other manifestations of VHL (2-4).

Haemangioblastomata are benign, highly vascular and often cystic tumors. They develop most often in the posterior fossa and rarely in the spinal cord and supratentorially (8). They are circumscribed but not encapsulated. As seen in our case, they are usually cystic with a solid tumor mural nodule, which is composed of blood vessels of various sizes and shapes lined by a single layer of endothelium. The space amongst the vascular channels is filled with stromal cells, which are now regarded as the principal tumor component. In addition, there are macrophages and reactive astrocytes. Haemangioblastomas are currently classified under 'tumor of uncertain origin', because the origin of stromal cells is not settled yet. In our case the stromal cells were diffusely positive for vermentin, and focally for S100 and NSE. Neuroendocrine origin was suggested, because of positive staining for neurone specific enolase, synaptophysm and neuropeptide Y in some cases (9).

Astrocytic origin was also suggested, because of variable GFAP positivity demonstrated in stromal cells. The only consistent finding was vimentin positivity. The endothelial marker was positive only in the endothelial cells lining the vessels. These findings suggest that stromal cells were heterogeneous and this included entrapped astrocytes (10). The stromal cells (not the endothelial cells) are known to secrete vascular endothelium growth factor (VEGF) which plays an important role in endothelial proliferation occurring in haemangioblastoma (11).

On histopathological examination, the most frequent differential diagnosis of haemangioblastoma is metastatic renal cell carcinoma (RCC), which may be associated with VHL. In our case, the structural pattern did not support the diagnosis of metastatic RCC and was confirmed by EMA immunostaining, which was negative in these tumor cells.

There are at least three phenotypes of VHL proposed by the United States National Cancer Institute (NCI) (Table 2). The most common is VHL type 1, which includes retinal and CNS haemangioblastoma, renal cysts and renal cell

Figure 2: Axial CT scans of the abdomen post IV contrast showing multiple cystic lesions within the pancreas and lesions suggestive of (Lt) hypernephroma. Note a large cortical cyst (Lt) kidney (arrow).

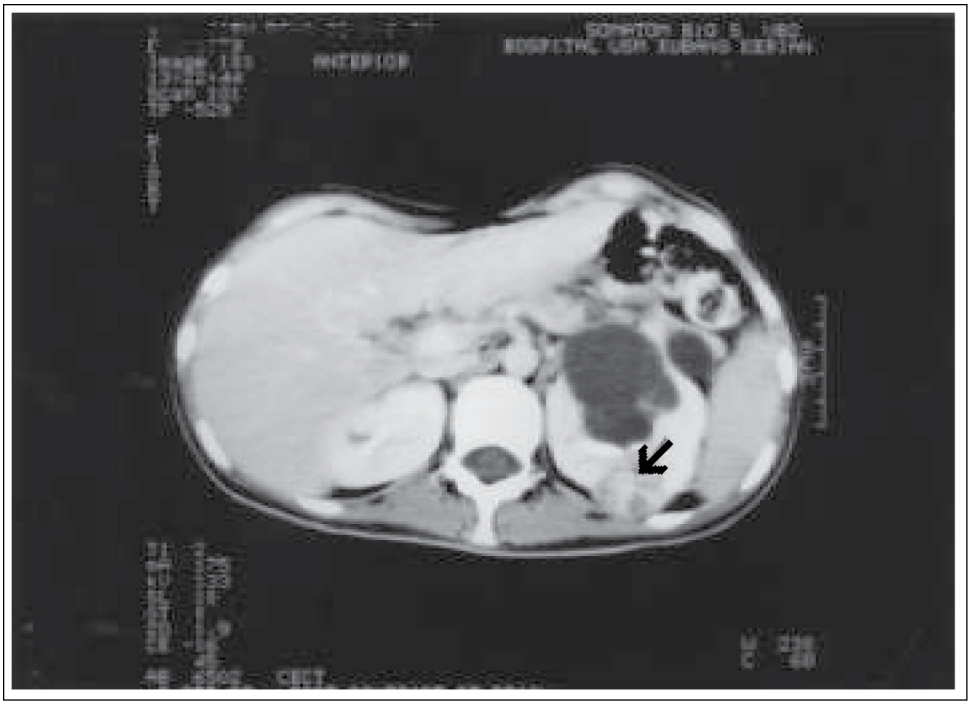
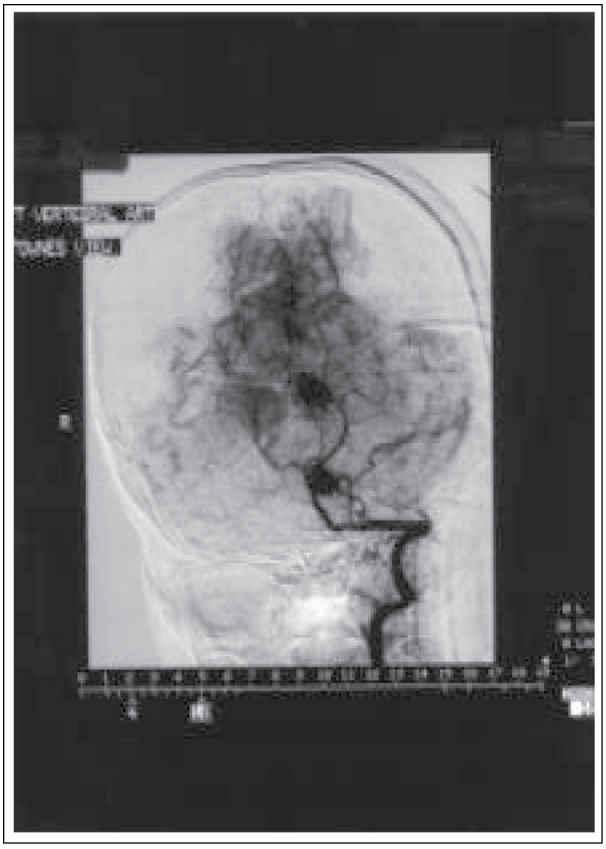


Figure 3: Left vertebral angiogram showing multiple areas of tumour blushes.



carcinoma and pancreatic cysts but no phaeochromocytoma. The second most common pattern of VHL also includes retinal and CNS haemangioblastoma, but additionally exhibit phaeochromocytoma and islet cell tumor of pancreas. The most usual phenotype of VHL (type 2B) manifests with retinal and CNS haemangioblastoma, phaeochromocytoma, renal and pancreatic diseases. The patient reported here belongs to VHL phenotype 1. Polycythaemia occurs in 5 to 30% of patients, harbouring a haemangioblastoma in the posterior fossa.

Table 2: NCI Classification of VHL[4]

Type 1: VHL without phaeochromocytoma
Type 2: VHL with phaeochromocytoma
A. Phaeochromocytoma and Retinal CNS haemangioblastoma
B. Phaeochromocytoma and Retinal CNS haemangioblastoma, Renal Cancer and pancreatic involvement.

The best imaging technique to diagnose haemangioblastoma is contrast enhanced MRI (1). Hence screening for VHL should include at least, pre and post contrast weighted images of the brain

Figure 4. *Axial MRI of the brain T1W1 post gadolinium showing multiple enhancing nodules in the (Lt) cerebellar hemisphere. Midline nodule is due to lesion in the cerebellar vermis.*

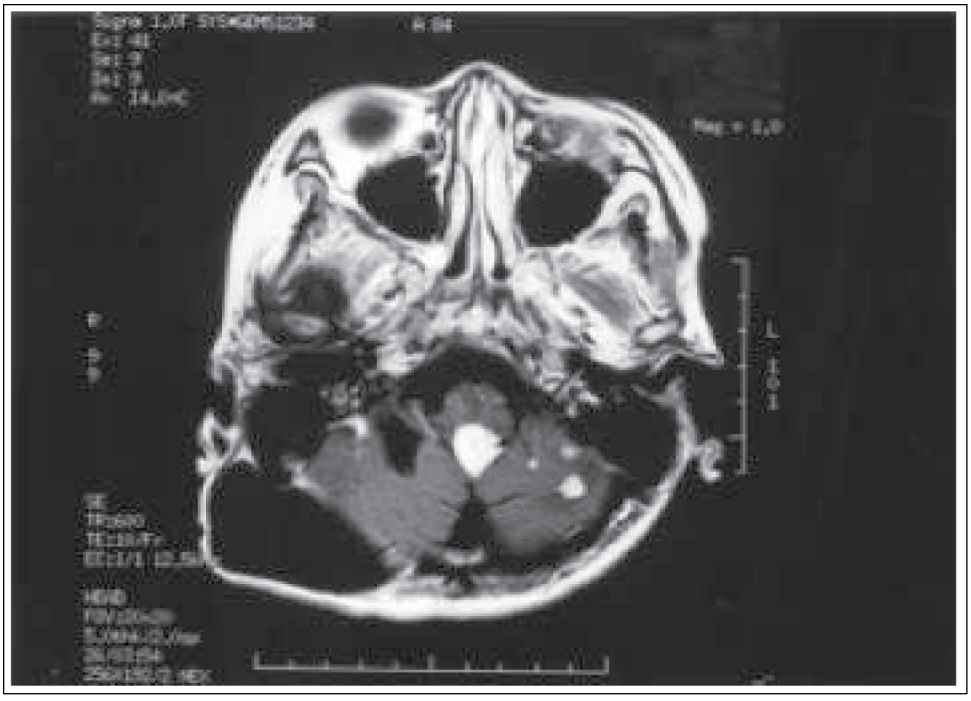
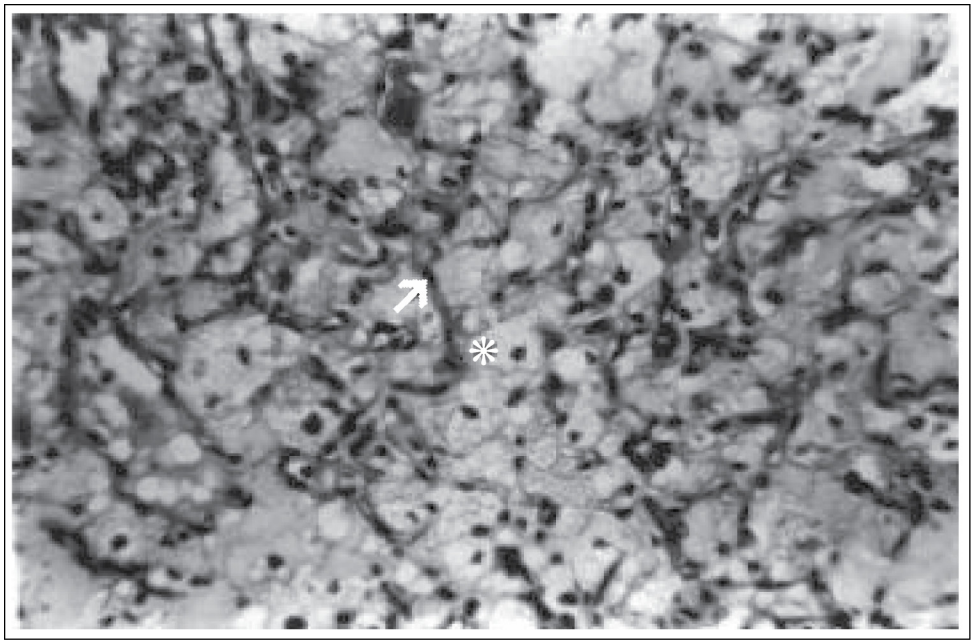


Figure 5: The tumour composed of anastomosing capillary network (➔) with interspersed vacuolated stromal cells (*) (H&E; 400x).



and spinal cord with thin sections through the posterior fossa and spinal cord. Angiography is commonly performed prior to surgery to demonstrate feeding vessels. The nidus of the tumor typically demonstrates a homogenous blush. Early venous drainage is frequently present in angiograms of haemangioblastoma.

The primary treatment is surgical removal of symptomatic lesions. Simple drainage of the cysts without removing the tumour nidus is ineffective. Intra-operative color Doppler has been useful in demonstrating the cysts, tumour mass and vessels of the lesions. Intratumoral alcohol injection during surgery (13-14) or 24 hours before operation (15) has been tried to embolise the feeding vessels. In non-operable patients or patients with residual tumor, external beam radiation has been used to arrest the progression of the disease or symptoms (16). Gamma Knife radio surgery has been reported as effective against the solitary small or medium sized mural nodule of haemangioblastoma while the cystic component requires repeated evacuation (17).

The median age of survival is 49 years and death commonly results from neurological complications of cerebellar haemangioblastoma (53%) or metastatic renal cell carcinoma (32%) (1).

Conclusion

von Hippel-Lindau disease is characterized by haemangioblastoma involving the retina, central nervous system and viscera. Haemangioblastoma of the central nervous system can be demonstrated in approximately 72 % of VHL patients. The site of predilection includes the cerebellum (52%), spinal cord (44%) and brain stem (18%)(18). Visceral cysts commonly affect kidney, pancreas and epididymis. Multicystic renal disease occurs in 50% of patients and is usually asymptomatic (18-20). Nearly 25% of VHL patients will progress to renal cell carcinoma (10). Renal cell carcinoma associated with VHL disease develops at a younger age (mean age 43 years) and has no sex predilection. Ten percent of patients have phaeochromocytoma, which may be bilateral (21-22). Two-thirds of patients have retinal haemangioblastoma and about one in two have multiple lesions which are frequently bilateral. Mortality is due to complications of the disease process and must be dealt with accordingly.

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