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CASE REPORT

BIVENTRICULAR CENTRAL NEUROCYTOMA

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A case of biventricular neurocytoma is reported. A 36 year old Malay lady presented with headache of 8 months duration. Physical examination revealed signs of increase intracranial pressure. CT-scan and MRI showed tumour in both lateral ventricles. Patient underwent tumour debulking followed by adjuvant radiotherapy. The radiological appearances of central neurocytoma are discussed.

Key words : *Central neurocytoma, treatment, radiology.*

Case report

A 36-year old Malay lady presented with an 8-month history of frontal headache which was throbbing in nature. There was no history of blurring of vision, nausea, numbness, vomiting, trauma, loss of weight, loss of appetite or neck stiffness. Prior to admission, the headache became more frequent and severe and was not relieved by analgesics. Her husband noticed a change in her behaviour. She had no previous significant medical history. Her social and family history were unremarkable.

On examination, the patient was alert and conscious. The vital signs were normal. Funduscopic examination revealed papilloedema on the left side. Other systems were essentially normal. Routine

Figure 1*: Axial NCCT brain reveals lobulated mass in both lateral ventricles. The mass has solid and cystic components.*

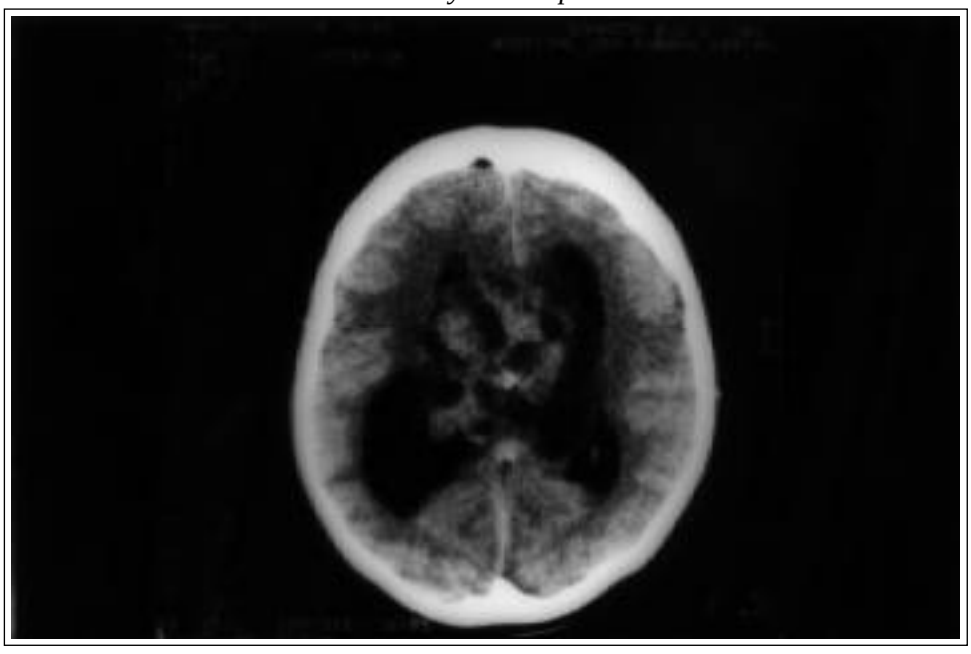
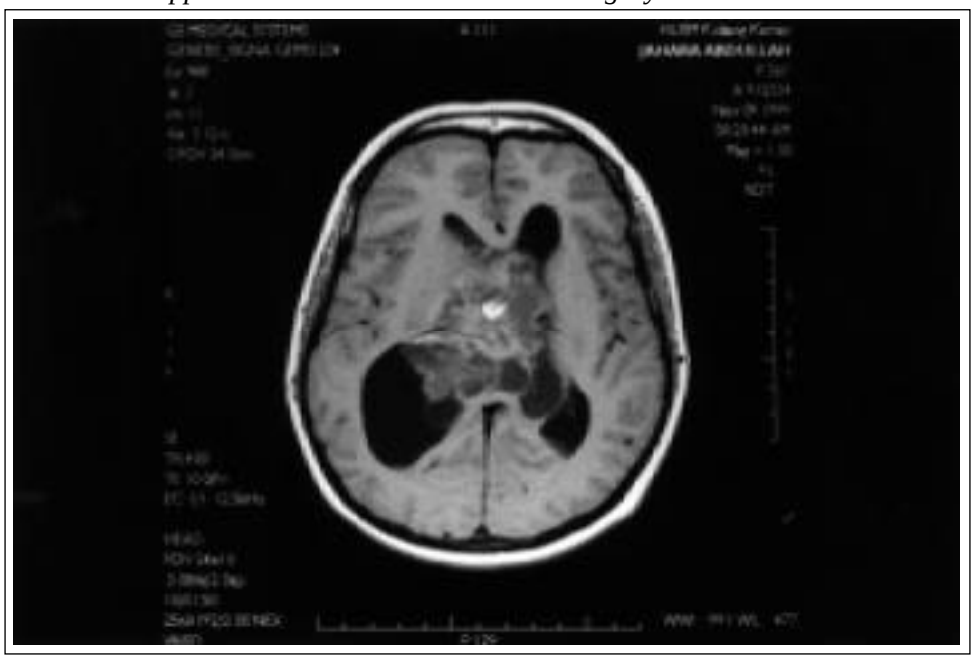


Figure 2: Axial T1WI shows lobulated mass in both lateral ventricles which appear to be isointense to the cortical gray matter.



blood investigations were also within normal limits.

Computed tomography (CT-scan) revealed a lobulated mass predominantly in the body of both lateral ventricles associated with hydrocephalus (Figure 1].

Areas of coarse calcification were not seen on CT-scan as expected in intraventricular neurocytoma. Attachment to the septum pellucidum could not be ascertained.

Magnetic resonance imaging revealed alobulated mass in both lateral ventricles which was of isointense signal intensity relative to cortical gray matter on T1WI (Figure 2). The mass showed evidence of cystic spaces and vascular flow void areas on T2WI (Figure 3). MRI appearance suggested an attachment of mass to the septum pellucidum (Figure 4). There were no evidence of haemorrhage. The solid component enhanced intensely following intravenous gadolinium (Figure 5).

Figure 3: Axial T2WI reveals cystic spaces and vascular flow void areas. Note the isointense solid component (arrow).

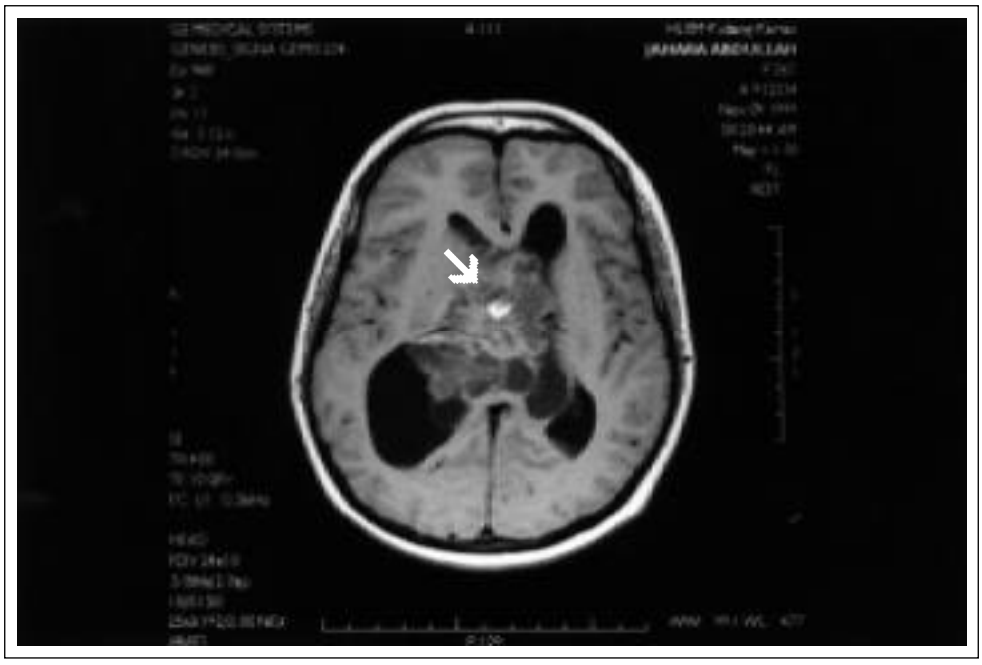
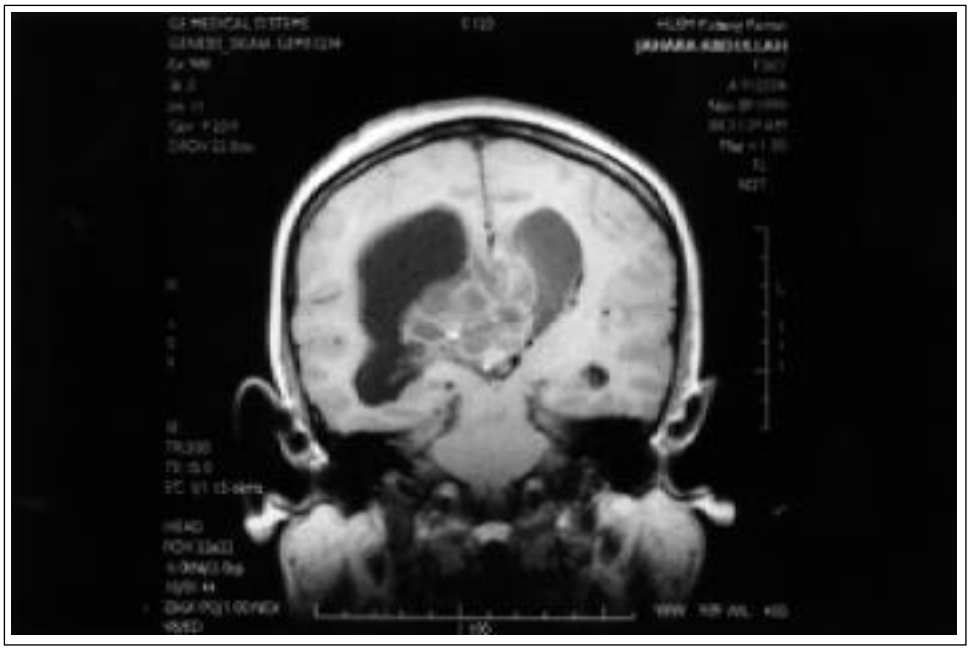


Figure 4. Coronal TIWI shows biventricular mass attached to the septum



Cerebral angiography revealed a lesion supplied by the branches of right anterior cerebral and middle cerebral arteries (Figure 6). There were no supply from the anterior or posterior choroidal arteries. Immediate treatment with intravenous dexamethasone and Rickham's catheter insertion were initiated to reduce the intracranial pressure.

Subsequently, the patient underwent tumour debulking. Histopathological examination showed uniform round cells with central nuclei, clear cytoplasm and well defined cell membranes. Immunohistochemical staining for glial fibrillary acid protein (GFAP) and synaptophysin were positive.

The post-operative course was complicated by an extradural haematoma which was completely evacuated.

In view of the residual tumour, she was subjected to radiotherapy, with a total dose of 54 Gy in 27 fractions over 6 weeks.

Discussion

Figure 5. Coronal T1WI post gadolinium DTPA shows enhancement of the solid component.

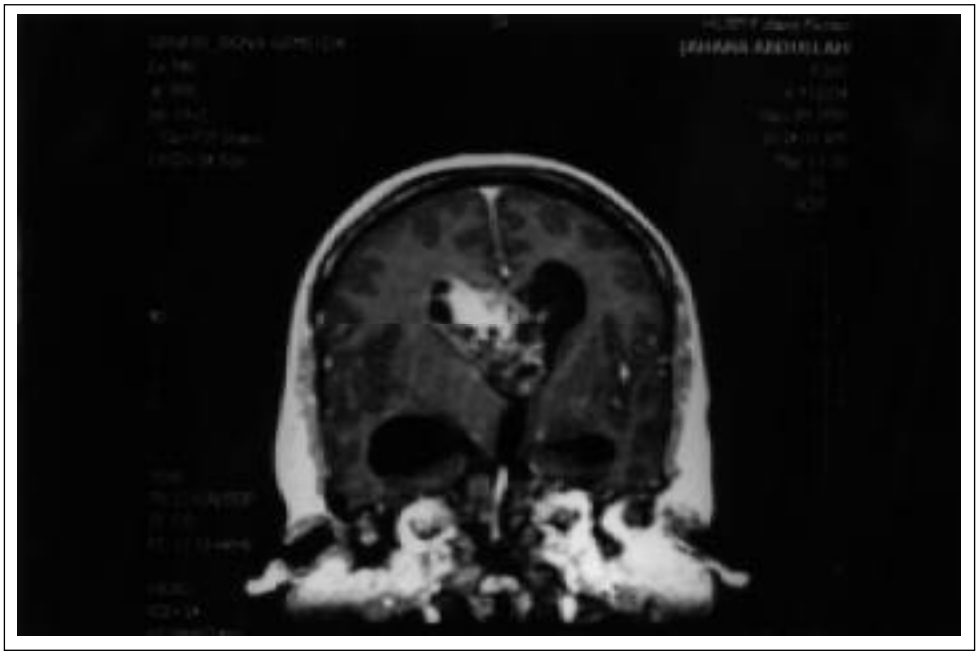
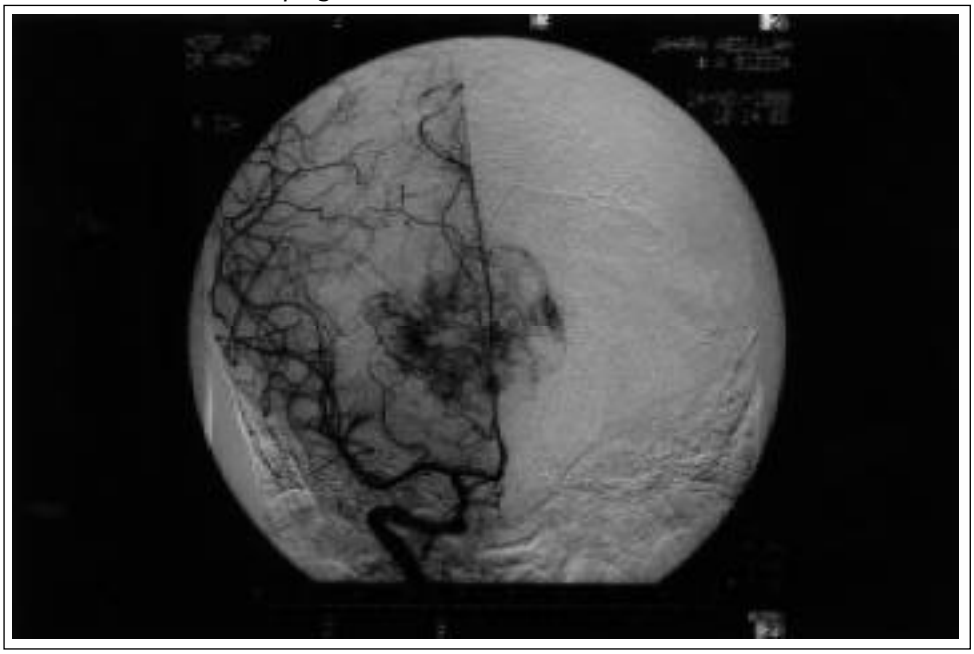


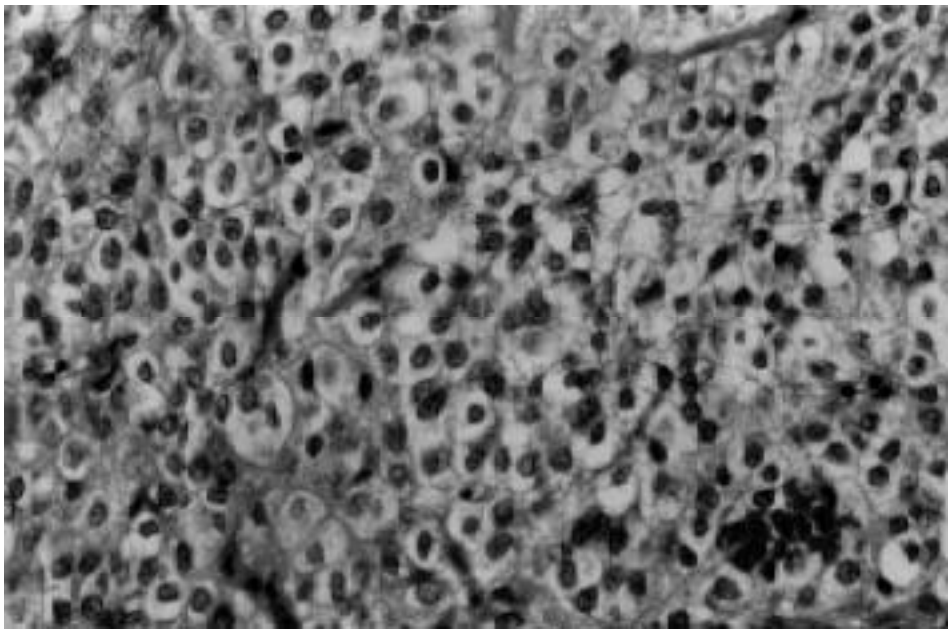
Figure 6: Right internal carotid angiogram reveals lesion supplied by the branches of right ACA and MCA.



Central neurocytoma is a small cell neuronal tumour that occurs in the lateral and third ventricles (1). It is composed of mature neuronal cells, giving an exception to the rule that neuronal cells do not replicate after fetal life. It was described previously by Hassoun et. al (2). However it was erroneously labelled as intraventricular oligodendroglioma. Following that it was termed as central neurocytoma by the World Health Organisation (3).

Typically the tumour presents in young adults (mean age : 25-30 years). The patient usually presents with nausea, vomiting, headache and papillooedema due to obstructive hydrocephalus (4). Commonly the lesion is intraventricular and attached to the septum pellucidum. It is a slow growing benign tumour, usually without extraventricular extension. A few unusual cases of extraventricular

Figure 7: Microscopic appearance of neurocytoma. Haematoxylin and Eosin, x 400.



extension have been reported (5).

Diagnosis

The general management guidelines for central neurocytoma are not yet clearly defined. The typical CT appearance of central neurocytoma is that of a coarsely calcified, well circumscribed intraventricular tumour found in the body or frontal horn of the lateral ventricle. It is usually in close proximity to the foramen of Monro and typically attached to the septum pellucidum (6). There may be bleeding within the tumour mass and hydrocephalus is almost always present. The tuntur enhances mild to moderate with intravenous contrast.

The tumour is mainly isointense to cortical gray matter on both T1 and T2WI. They may have cystic spaces and calcification, giving rise to signal void areas or heterogenous intensity within the tumour mass. Magnetic resonance imaging is an excellent modality in demonstrating the characteristic attachment of the tumour to the septum pellucidum (7). There is no specific angiographic feature for central neurocytoma. Computed tomography still plays a very important role especially in demonstrating the calcification within the tumour.

Histologically, the tumour has a uniform appearance of small, round cells that mimics

Table 1: Differential diagnoses of an intraventricular tumour

Tumour/ Features	Central Neurocytoma	Meningioma	Choroid plexus papilloma	Oligodendroglioma	Ependymoma
Origin	Mature neurons	Meningothelial cells concentrated in arachnoid villi.	Choroid epithelium	Oligodendrogliocytes ±Astrocyte	Intraventricularly/Ependymal rest in the white matter
Age	Young adult (25-30) years	35-75years		Any age.Most 4-5D	Predominantly <5y.o Smaller peak in 3rdD
Sex(M:F)	-	M>F	3:2	5:4	0.8:1
Location	Body±frontal horn+3rd Ventricle	Exclusively in trigone	Adult:3rd v/4th V Children:Trigone	Frontal>Temporal> parietal> brainstem. Less commonly extension into thesubarachnoid space	Infratentorial:Floor of 4th V. Supratentorial:Frontal> parietal>temporo-parietal.
CT	Well circumscribed. Coarsely calcified. Mild-moderate contrast enhancement. Peritumoral oedema extremely uncommon	Sharply marginated Intense contrast enhancement Calcification in radial/circular pattern 20%	Well demarcated Smooth/ Lobulated. Homogenously increase density. Dense homogenous enhancement. Small foci of Ca2+(common) N/B:Other masses can be noted within plexus i.e AVM Cavernous haemangioma Dermoid Epidermoid	Mixture of hypodensity, isodensity, calcification and occasionally haemorrhage. Cystic areas due to myxoid accumulation. Ca2+ 91% especially where the tumour has infiltrated the cortical grey matter (nodular/massive/ dotdash/curvilinear/stippled/ diffuse) Calvarial erosion	Isointense on plain CT. Frequently but not always, show contrast enhancement. Ca:50%. Small seeding into the ventricular ependyma, subarachnoid space and spinal canal do not show contrast enhancement until the tumour reaches a certain degree of enlargement.
MRI	Isointense relative to cortical grey matter on T1&T2WI with heterogenous areas due to calcifications, cystic spaces or vascular flow voids. Attach to septum pellucidum (characteristic)	Hypo-iso onT1 Iso-hyper on T2	Hypo- to- isointense to brain on all pulse sequences. Hypo-Ca/Vascular signal void. Intense enhancement. (Ideal method to demonstrate cerebellar/ brainsteminvasion.	Heterogenous on all pulse sequences. Hyperintensity from previous haemorrhage may be noted on T1WI.	Low on T1WI. High on T2WI. Mixed signal due to haemorrhage, calcification and blood vessel.
Angio	Supply from striate arteries of MCA, Anterior Choroidal and branches of ACA.	'mother in law' sunburst/spoke-wheel pattern. Supply : choroidal vessel	Dilatation of PICA/ Choroidal branches. Dense tumour stain in arterial phase.	The fine capillary meshwork is too small to be seen on angio.	
Prognosis after diagnosis and treatment		Cx: Local invasion of venous sinuses.	Papilloma is often totally resectable, while a carcinoma, because of invasion, is not. Long term survival of patient with choroid plexus papilloma.	<50% at 5 years	Wrap around the blood vessel and cranial nerve making total resection difficult. Tended to recur locally and disseminate with time.

oligodendroglioma, but central neurocytoma is purely neuronal in origin. Presence of neuronal tissue can be shown by electron microscopy or neuronal specific markers such as synaptophysin (8).

The differential diagnoses of an intraventricular tumour based on radiological findings are many (Table 1). However, central neurocytoma should be considered as the main differential diagnosis in a young adult with a calcified intraventricular mass attached to the septum pellucidum. The possible diagnosis of central neurocytoma based on radiological features should be noted to the pathologist since further staining will be required to arrive at the correct diagnosis.

The general management guidelines for central neurocytoma are not yet clearly defined. However from the summary of published literature, it is evident that, tumour debunking surgery should be the initial treatment modality. The completeness of surgery predicts post treatment outcome. Though central neurocytoma is a benign tumour, repeated recurrence and CSF spread of disease can occur. There are clear indications that local radiotherapy help to reduce local relapse rate.

Response to radiation is usually slow as it is a benign disease. The shrinkage of tumour following radiotherapy takes almost 6months to 2 years post treatment (9). Recently there is a report of use of combination chemotherapy in recurrent central neurocytoma (11). However it's efficacy has yet to be proven.

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References

1. Figarella-Branger D, Pellissier JF, Daumas-Duport C, Delisle MB, Pasquier B, Parent M, Gambarelli D, Rougon G, Hassoun J. Central Neurocytoma: Critical evaluation of small-cell Neuronal Tumour. *Am J Surg Pathol* 1992; **16(2)**: 97-109
2. Hassoun J, Gambarelli D, Toga M. Central Neurocytoma. An electron microscopic study of two cases. *Acta Neuropathol* 1982; **56**:151-56
3. World Health Organisation (WHO) *Book for "Histological Typing of Tumours of the Central Nervous System*, 1993.
4. Dong Gyu Kim, Je G. Kim DG, Chi IG, Park SH, Lee SH, Jung HW, Kim HJ, Cho BK, Choi KS, Han DH. Intraventricular neurocytoma: clinicopathological analysis of seven cases. *J. Neurosurg* 1992; **76**:759-65.
5. Eng DY, De Monte F, Ginsberg L, Fuller GN, Jaeckle K. Craniospinal dissemination of central neurocytoma. Report of two cases. *Neurosurg* 1997; **86**:547-52.
6. Yasargil MG, Von Ammon K, Von Deimling A, Valvanis A, Wichmann W, Wiestler OD. Central neurocytoma. Histopathological variants and therapeutic approaches. *J. Neurosurg* 1992; **76**:32-37.
7. Kim DG, Kim JS Chi JG, Park SH, Jung HW, Choi KS, Han DH. Central neurocytoma: proliferative potential and biological behaviour. *J Neurosurg.* 1996; **84**:742-47.
8. Jay V, Edwards V, Hoving E, Rutka J, Becker L, Zielenska M, Teshima I. Central neurocytoma: Morphological, flow cytometric, polymerase chain reaction, fluorescence in situ hybridization and karytypic analyses. *J. Neurosurg* 1996;**90**:348-54.
9. Kim DH, Paek SH, Kim IH Chi JE, Jung HW, Han DH, Choi KS, Cho BK. Central neurocytoma: The role of radiation therapy and longterm outcome. *Cancer* 1997;**79**:1995-2002.
10. Weil MD, Wara WM. Pediatric tumour of the central nervous system. In Leihel SN and Philips TL eds. *Textbook, of radiotion oncology*. WB Saunders company. Philadelphia, 1998; 934-35.
11. Brandes AA, Amista P, Gardiman M Volphin D, Guylielmi B, Carolloc, Pinnag, Turazzis, Momfardini's. Chemotherapy in patients with recurrent and progressive neurocytoma. *Cancer* 2000; **88**:169-74

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CASE REPORT

THE TRIAD OF LICHEN PLANUS, THYMOMA AND LIVER CIRRHOSIS-HEPATOMA. FIRST REPORTED CASE

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We describe a patient with liver cirrhosis who presented with erosive oral and cutaneous lichen planus (LP) and incidentally was found simultaneously to have thymoma and hepatoma. We support the notion forwarded earlier that LP and chronic liver disease is more than a mere coincidence and that there is a non-coincidental association between LP and thymoma. We believe this is also the first reported case in the English Literature of coexistence of the three condition LP, thymoma and hepatoma complicating liver disease.

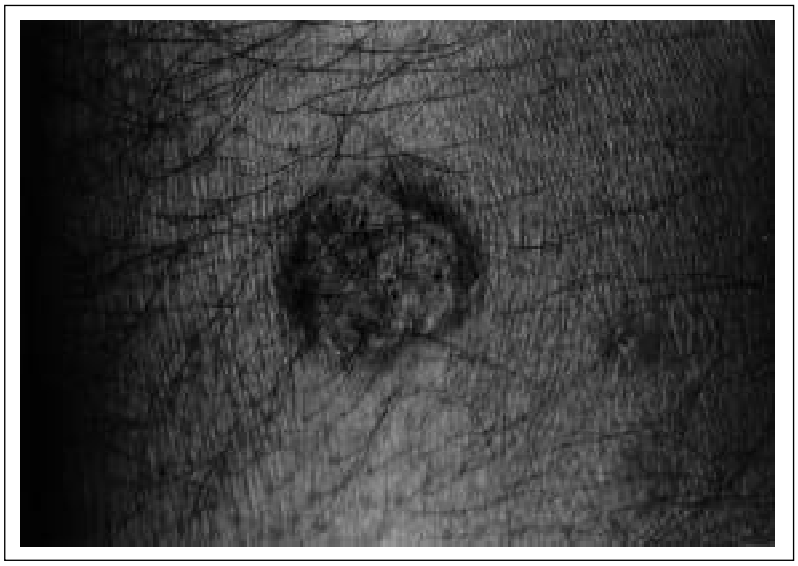
Key words : *Lichen planus, thymoma, chronic liver disease*

Introduction

The relationship between Lichen Planus (LP) and liver disease and LP and thymoma has been reported before (1-7), however a cause and effect relationship is still controversial.

This observation has interested clinicians and stimulated attempts to explain the phenomenon. There is evidence that LP is immune mediated. Immune reactants are found at the basement membrane zone on direct immunofluorescence, the infiltrate are predominantly of helper T cells and

Fig.1 : Intensely pruitic purplich plaque with whitich surface (Wickham's striae) on the anterior aspect of the shin, this lesion is typical of lichen palnus



LP has been observed combined with other autoimmune diseases such as alopecia areata, vitiligo, pemphigoid and systemic lupus erythematosus.

The thymus itself on the other hand plays a key role in the immunologic status of an individual and an association of disorders of the thymus with autoimmune diseases may occur.

Here we present a rare and interesting combination of lichen planus and both the immunologically mediated disease thymoma and liver cirrhosis complicated by a hepatoma.

Case report

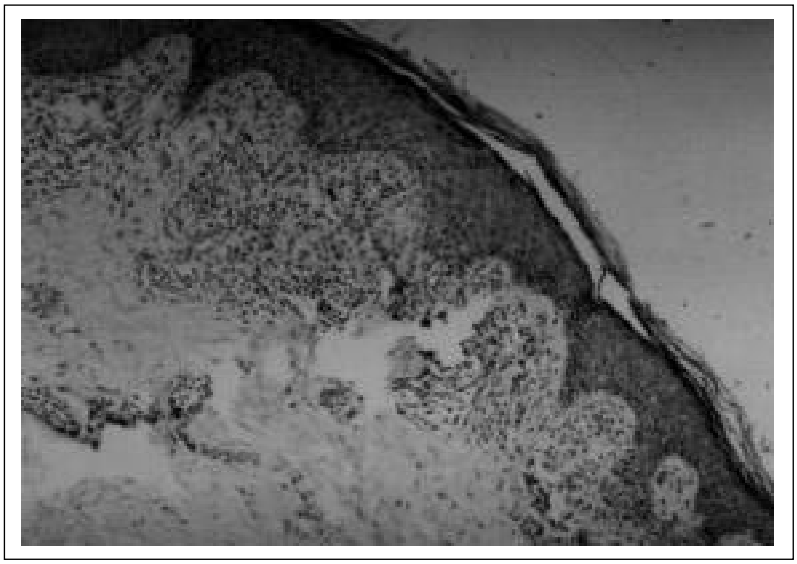
A 59 year old man, retired driver in the army, presented to the outpatient clinic of Universiti Kebangsaan Malaysia on 12th Sept 1994 with complaint of painful oral lesion for one month. This was followed two weeks later by onset of pruritic rash distributed on both upper and lower limbs. Prior to this, he was well and was not known to have any medical illnesses. He denied any loss of weight despite having problems with taking solid food due to oral ulcer.

On examination, there was erosive LP on his buccal mucosa, tongue and lips. There were also multiple discrete, intensely pruritic, purplish papules and plaque on the anterior aspect of his shins (Fig. 1), flexor aspect of his wrists and forearm bilaterally and these lesions were typical of LP. He was noted to be pale and there were palpable deep cervical lymph nodes. He also had hepatomegaly with liver span of 4cm below right costal margin and splenomegaly extending medially 6cm below left costal margin. There was no sign of myasthenia gravis.

Investigations and progress

Full blood picture showed that he has normochromic anemia with low hemoglobin level 11.4 g/dL and his platelet count was 1.52 x 10^5/cubic mm. The level of his serum iron and TIBC were low at 5.5 umol/L and 42 umol/L (normal) respectively. His liver function tests were deranged, his total protein and albumin were low at 54 g/L and 29/L respectively and serum alkaline phosphatase level was raised at 159 U/l. However, his serum alanine amino transferase, serum bilirubin, serum calcium and serum phosphate level were normal. His prothrombin time was prolonged at 16.3 seconds compared to 11.7 seconds (control). Serum creatinine, potassium, sodium and blood urea were all normal. No organism was cultured from the oral mucosa despite repeated attempts. Interestingly, hepatitis B surface antigen tested from his blood was positive and he had repeatedly markedly elevated alpha feto protein level at 3760 ng/ml. Collagen screening was also done, his antinuclear factor was

Fig.2 : Histopathology of the skin lesion (biopsy taken from the forearm) under low power view on H&E stain showed hyperkeratosis, hypergranulosis and acanthosis with irregular elongation of rete ridges forming saw-tooth appearance. The dermis showed band-like dermal infiltrate of mainly lymphocytes



positive (homogenous pattern) but his rheumatoid factor, anti DNA and LE cells were repeatedly negative. His ESR was only 16mm per hr. His chest radiograph showed upper mediastinal widening.

Skin biopsy on his right forearm confirmed the clinical diagnosis of LP. The histology of the skin (Fig. 1) showed hyperkeratosis, hypergranulosis and acanthosis with irregular elongation of rete ridges forming saw-tooth appearance. The dermis showed band-like dermal infiltrate of mainly lymphocytes and there was degeneration of the basal layer with moderate pigmentary incontinence. Colloid bodies in the upper dermis stained strongly for IgM.

Ultrasound of the liver, showed liver cirrhosis, splenomegaly and ascites. Computed tomography (CT) of the thorax (Fig. 3) and abdomen revealed a large solid anterior mediastinal mass 9 X 5 X 14 cm. The great vessels and the arch of the aorta were displaced posteriorly. The diagnosis of thymoma was considered.

CT revealed the liver to be inhomogeneous with multiple hypodense nodules seen in both lobes. The liver outline was lobulated and irregular (see fig 4). In view of the markedly raised alpha-fetoprotein levels and positive test for Hepatitis B surface antigen, a diagnosis of hepatoma with underlying liver cirrhosis and portal hypertension was made.

CT guided fine needle aspiration biopsy of the mediastinal mass was performed. Histological examination confirmed the diagnosis of thymoma. The tumour was cellular. The cells had hyperchromatic oval nuclei with indistinct cytoplasm and stained positively for cytokeratin. These cells forms rosette pattern in many areas stained negatively to neurone specific amylase. In view of the invasive nature of the anterior mediastinal mass, it was diagnosed as a malignant thymoma.

Fine needle aspiration performed at the same time under CT guide confirmed the diagnosis of liver cirrhosis. The hepatic parenchyma was divided into lobules by fibrous tissue septa, which was infiltrated by lymphocytes. There was bile duct proliferation. The hepatocytes showed regeneration with large nuclei and some of them were binucleated. However, no malignant cells were seen.

His erosive oral and skin lesion remained a problem. He succumbed two months later.

Discussions

Our patient has erosive LP, thymoma and liver cirrhosis. Although raised serum alpha-fetoprotein in the presence of Hepatitis B antigenemia could be related to other liver condition such as chronic active hepatitis, cirrhosis and acute hepatitis (8) however it is unlikely in this case because this level is too high. Besides he did not have evidence of acute hepatitis or acute liver failure as suggested by his normal transaminases levels. The other possibility is that his liver nodule could be a macroregenerative nodule. Macroregerative nodules in liver cirrhosis are however not associated with elevated serum alpha-fetoprotein (9). Therefore, although there was

Fig.3 : Caption for the CT images: CT thorax: a large solid tumour (arrowed) in the anterior mediastinum displacing the arch of the aorta (asterisk) posteriorly

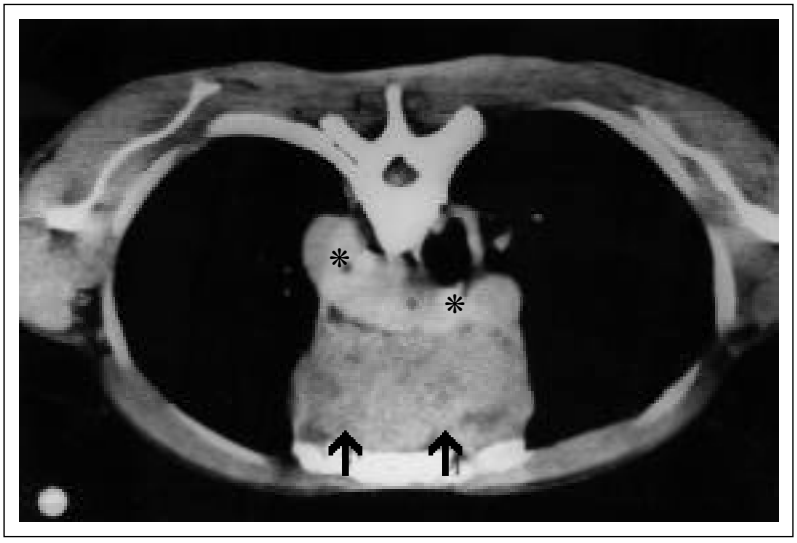
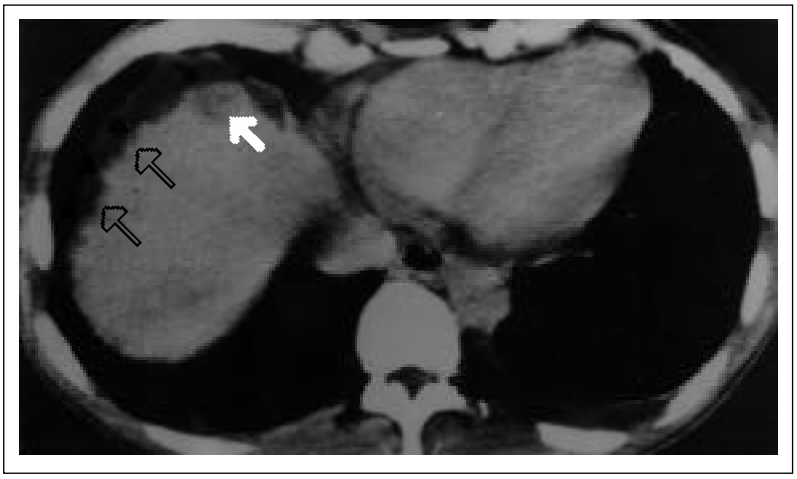


Fig.4 : Caption for the CT images: CT liver: Hypodense nodules in the right lobe (arrowed). The liver outline is irregular (arrowheads)



no histological confirmation of hepatoma, his markedly elevated serum alpha-fetoprotein of greater than 3000ng/ml in the presence of multiple liver nodules leave us in no doubt that he has hepatoma.

We are uncertain of the significance of antinuclear factor in the absence of clinical features of connective tissue disease in our patient, but similar observation of presence of positive antinuclear factor was noted in a patient with LP and thymoma by Ng (2). He also highlighted reports of at least 16 cases of SLE and thymoma. It is most probable that the thymus is the key factor in these deranged autoimmune phenomena

Gibson (3),in his review of cutaneous problem of 172 patients with thymoma found that 2 patients had LP. Tan (4), Aronson (5), Flamenbaum (6) and Mineo (7) reported separately four cases that had thymoma and LP. All these six patients had one striking similarity; they all had erosive painful oral LP, as did our patient. Two had thymoma that preceded LP, two had LP prior to the diagnosis and two had LP at the time of diagnosis of thymoma. To the best of our knowledge, up to date, there have been only two cases of combined hepatocellular carcinoma and LP reported (10). The occurrence of LP, thymoma, liver cirrhosis and hepatoma is exceedingly rare and has never been reported before, and we suggest that there is a probable association between these conditions. LP has been known to be associated with hepatitis B infection and liver cirrhosis (1,11-12). There is no doubt that liver cirrhosis in our patient is the end result of chronic active hepatitis from hepatitis B infection and this association has been addressed before by Rebora (13) who pointed out the remarkably similar histologic and immunologic features between LP and chronic active hepatitis and that the lichenoid infiltrate in the dermis is similar to T lymphocytes infiltration of the portal spaces destroying the normal architecture of the hepatic lobule. Since erosive LP is relatively uncommon, we suggest all patients with erosive lichen planus should be investigated for thymoma and liver disease.

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References

1. GISED, lichen planus and liver diseases. A multicentre case control study. *Br. Med. J.* 1990;**300**:227-30.
2. Ng PP. Ng SK. Chng HH. Pemphigus foliaceus and oral lichen planus in a patient with systemic lupus erythematosus and thymoma. *Clinical & Experimental Dermatology*. 1998;**23**:181-4.

3. Lawrence E. Gibson, Sigfrid A Muller. Dermatologic disorders in patients with thymoma. *Acta Derm Venereol (Stockholm)* 1987; **67**: 351-6.

4. Tan RS-H. Ulcerative colitis, myasthenia gravis, atypical lichen planus, alopecia areata, vitiligo. *Proc R Soc Med* 1974; **67**: 195-6.

5. Aronson IK, Soltani K, Paik K-I, Rubenstein D., Lorinz AL. Triad of lichen planus, myasthenia gravis and thymoma. *Archive Dermatol* 1978; **114**: 255-58.

6. Flamenbaum HS, Safai B, Seigal FP, Pahwa S. Lichen planus in two immunodeficient hosts. *J Am Acad Dermatol* 1982; **6**: 918-20.

7. Mineo TC, Biancari F, D' Andrea V. Myasthenia gravis, psychiatric disturbances, idiopathic thrombocytopenic purpura, and lichen planus associated with cervical thymoma *Journal of Thoracic & Cardiovascular Surgery*. 1996;**111(2)**:486-7.

8. Chen DS, Sung JL. Relationship of hepatitis B surface antigen to serum alpha-fetoprotein in nonmalignant diseases of the liver. *Cancer*. 1979; **44**:984-92.

9. Theise ND, Fiel IM, Hytiroglou P, Ferrell L, Schwartz M, Miller C, Thung SN. Macroregenerative nodules in cirrhosis are not associated with elevated serum or stainable tissue alpha-fetoprotein. *Liver*. 1995;**15(1)**:30-4.

10. A Virgili,E Robert, A Rebora. Hepatocellular carcinoma and lichen planus: Report of two cases. *Dermatology* 1992;**184**:137-38.

11. Ayala F, Balato N, Tranfaglia A, et al. Oral erosive lichen planus and chronic liver disease. *J Am Acad Dermatol* 1986;**14**:139-1.

12. Alfredo Rebora, Lichen planus and the liver, *The Lancet* 1981;**10**: 805-6.

13. Alfredo Rebora, Franco Rongioletti. Lichen planus and Chronic active hepatitis, a retrospective survey. *Acta Derm Venereol(Stockh)* 1984:**64**:53-6.

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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 6^{th} and left 8^{th} 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 4^{th} 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.

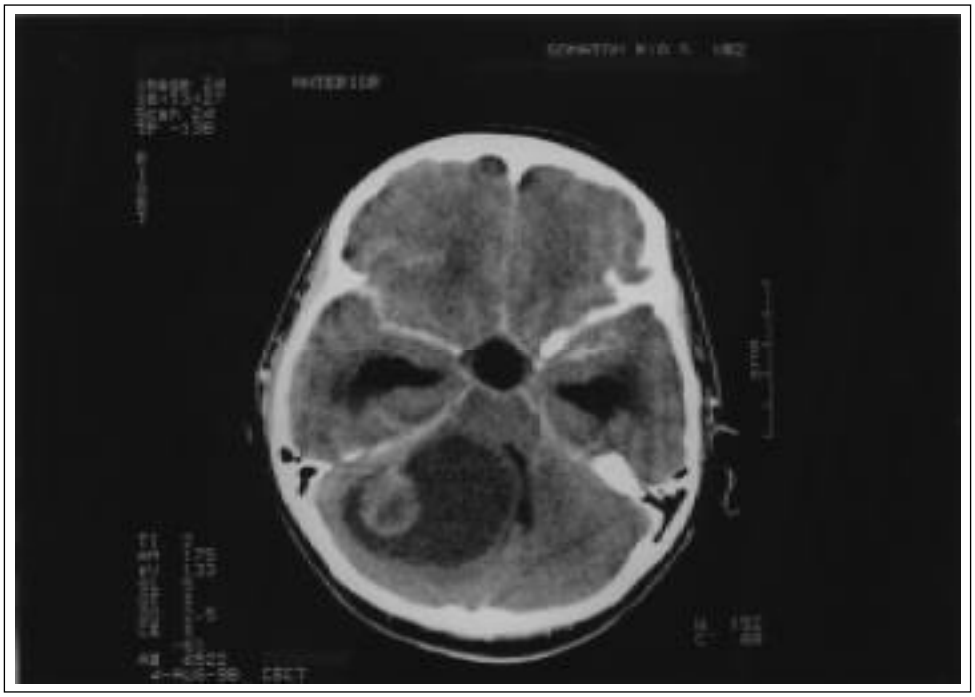
Table 1: Diagnostic features of von Hippel-Lindau Disease.

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).

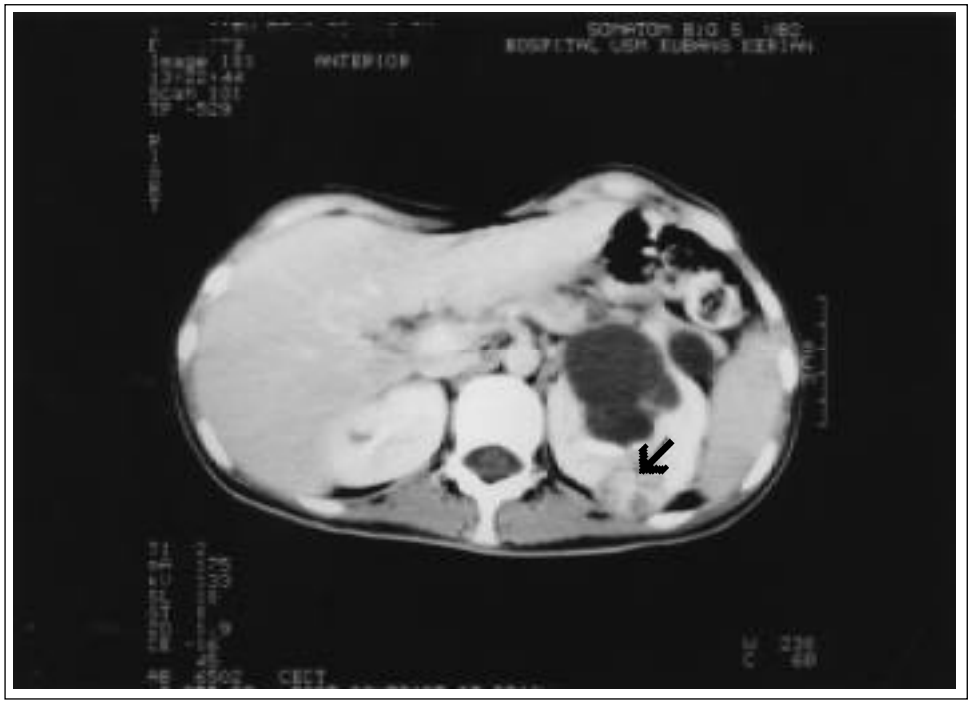
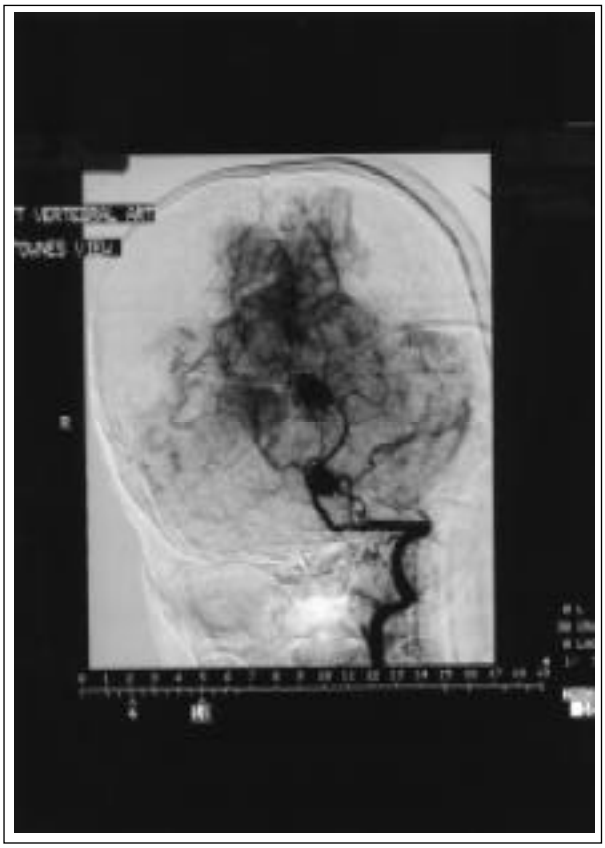


Figure 3: Left vertebral angiogram showing multiple areas of tumour blushes.



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.*

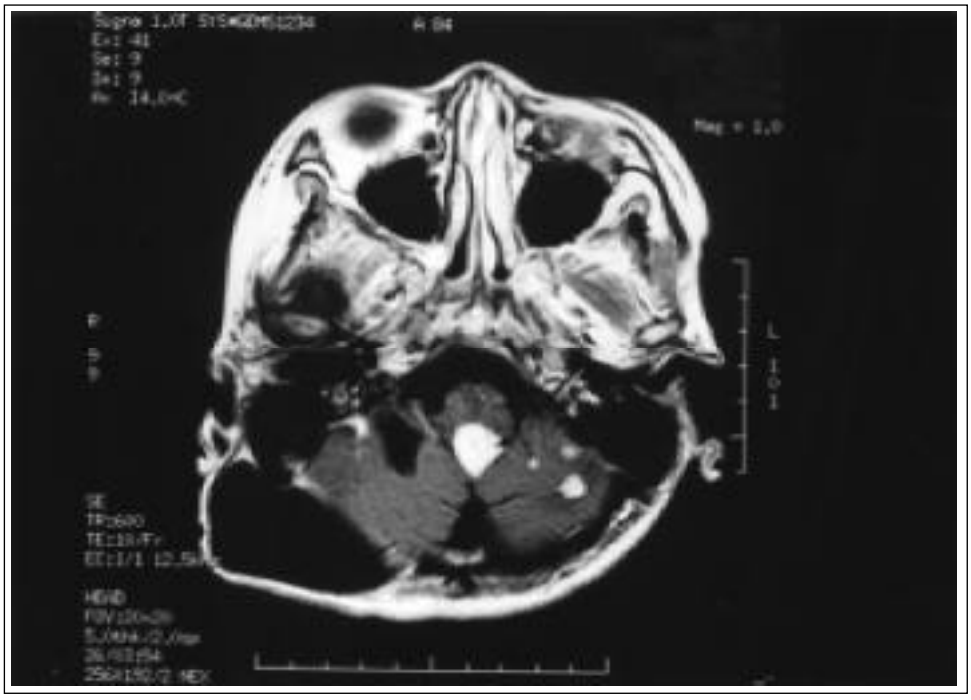
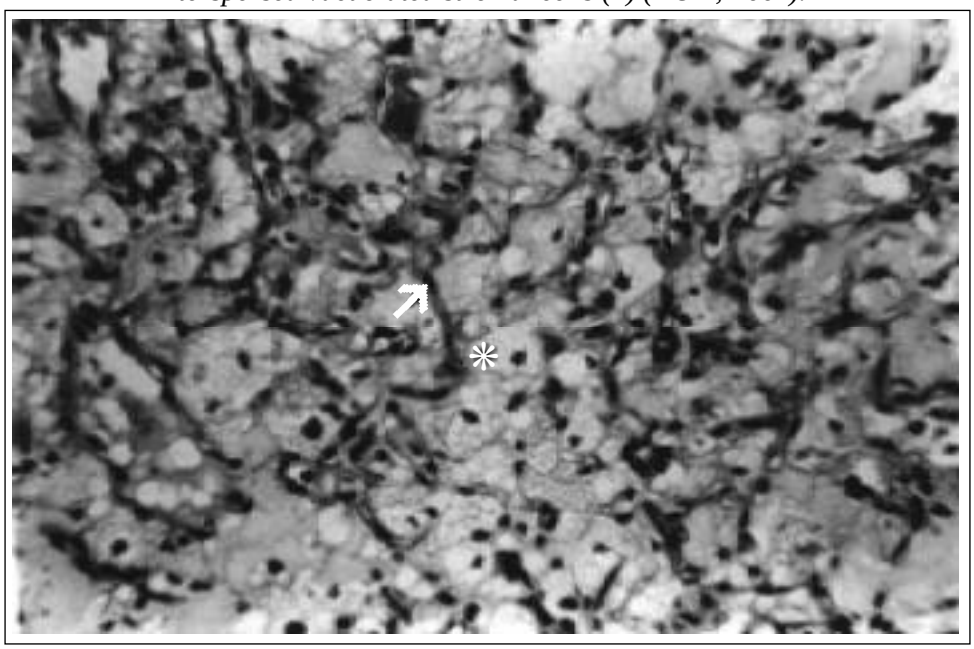


Figure 5: The tumour composed of anastomosing capillary network (➔) with interspersed vacuolated stromal cells (*) (H&E; 400x).



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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References

1. D Choyke PL, Glenn GM, Walther MM, Patronas NJ, Linehan WM, Zbar B. von Hippel-Lindau disease: Genetic, Clinical and Imaging Features. *Radiology* 1995; **194:**629-42.

2. Gumprecht HK, Lumenta CB. Multifocal hemangioblastoma in a young woman with Hippel-Lindau syndrome. *Zentrabl Neurochir* 1998;**59**:181-4.

3. Weinberg RA. Tumour suppressor genes. *Science* 1991;**254:**1138-46.

4. Richard S, Martin S, David P, Decq P. von Hippel-Lindau disease and central Nervous system hemangioblastoma. Progress in genetics and clinical management. *Neurochirurgie* 1998;**44:**258-66.

5. Jensen AM, Bisgaard ML. von Hippel-Lindau disease and molecular genetic diagnosis and molecular genetic diagnosis. *Ugeska Laeger* 1999;**161**:959-61.

6. Richard S, Giraud S, Beroud C, Caron J, Penfornis F, Baudin E, Niccoli-Sire P, Murat A, Schlumberger M, Plouin PF, Conte-Devolx B. von Hippel-Lindau disease : recent genetic progress and patient management. Francophone Study Group of Von Hippel-Lindau Disease. *Ann. Endocrinol (Paris)* 1998;**59:**452-8.

7. Webster AR, Maher AR, Bird Ac, Gregor Z J, Moore AT. A clinical and molecular 'genetic analysis of solitary angioma. *Opthalmology* 1999;**106**:623-9.

8. Grisolyi F, Gambarelli D, Raybaud C Suprasellar haemangioblastoma. *Surg Neurol* 1984;**22:**257-62.

9. Becker I, Paulus W, Roggendorf W. Histogenesis of stromal cells in cerebellar hemangioblastoma: an immunohistochemical study. *Am J Pathol* 1989; **134**:271-75.

10. Kepes JJ, Rengachary SS, Lee SH. Astrocytes in hemangioblastoma of the central nervous system and their relationship to stromal cells. *Acta Neuropathol (Berl)* 1979;**47**:99-104.

11. Morii K, Tanaka R, Washiyama K, Kumanishi T, Kuwano R. Expression of vascular endothelial growth factor in capillary hemangioblastoma. *Biochim Biophys Res Common* 1993;**194**:749-55.

12. Horton JC, Griffith R, Harsh IV, James W. Fisher, William F. Hoyt. Von Hippel Lindau disease and erythrocytosis: Radioimunoassay of erythropoiten in fluid from a brainstem hemangioblastoma. *Neurology* 1991;**41**:753-54.

13. Salome F, Colombeau P, Fermeaux V, Cazaux P, Dumas JP, Pfeifer P, Moreau JJ, Richard S, Labrousse F. Renal lesions in von Hippel-Lindau disease: the benign the malignant, the unknown. *Eur. Urol* 1998;**34(5)**:383-92.

14. Lonser RR, Heiss JD, Oldfield EH. Tumour devascularization by intratumoral ethanol injection during surgery Technical note. *J. Neurosurgery* 1998;**88:**923-4.

15. Vazquez-Anon V, Botella C, Beltran A, Solera M, Piquer J. Preoperative embolization of solid cervicomedullary junction hemangioblastomas: report of two cases. *Neuroradiology* 1997;**39(2)**:86-9.

16. Chakraborti PR, Chakrabarti KB, Doughty D, Plowman PN. Stereotactic multiple arc radiotherapy, IV-Hemangioblastoma. *Br. J Neurosurgery* 1997;**11:**110-15.

17. Niemela M, Lim YJ, Soderman M, Jaaskelainen J, Lindquist C. Gamma Knife radiosurgery in 11 hemangioblastomas. *J Neurosurgery* 1996;**85(4):**591-6.

18. Filling Katz MR, Choyke OL, Oldfield E, Charnas L, Patrona SNJ, Glenn EM, Goris MB, Morgan JK, Linehan WM, Seizinger BR. Central nervous systems involvement in Von Hippel-Lindau. *Neurology* 1991;**41**:41-6.

19. Persad RA, Probert JL, Sharma SD, Haq A, Doyle PT. Surgical management of the renal manifestations of von Hippel-Lindau disease: a review of a United Kingdom case series. *British Journal of Urology* 1997;**80**:392-96.

20. Neumann HP, Bender BU, Berger DP, Laubenberger J, Schultze-Seemann W, Watterauer U, Ferstl FJ, Herbst EW, Schwarzkopf G, Hes FJ, Lips CJ, Lamiell JM, Masek O, Riegler P, Mueller B, Glovac D, Brauch H,. Prevalence, morphology and biology of renal cell carcinoma in von Hippel-Lindau disease compared to sporadic renal cell carcinoma. *Urology* 1998;**160**:1248-54.

21. Curley SA, Lott ST, Luca JW, Frazier ML, Killany AM. Surgical decision-making affected by clinical and genetic screening of a novel kindred with von Hippel-Lindau disease and pancreatic islet cell tumors. *Ann. Surg* 1998;**227:**229-35.

22. Torres VE, Bjornsson, Zincke H. Inherited renal neoplasms. *J. Nephrol* 1998;**11:**229-38.