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Clinical Records

Von Hippel-Lindau disease associated with an invasive choroid plexus tumour presenting as a middle ear mass

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Abstract
Cerebellar haemangioblastomata and angiomata of the retina are the most common vascular tumours seen in von Hippel-Lindau disease. A definite association between this condition and choroid plexus tumour has not been described previously and its presentation as a middle ear mass is unique.

Introduction

Von Hippel-Lindau (VHL) disease is a rare autosomal dominant hereditary disorder with variable penetrance characterized by vascular tumours involving the brain, eyes and kidney (Huson *et al.*, 1986; Neumann, 1987a). Cerebellar haemangioblastomata and angiomata of the retina are the most common manifestations, but cerebral and spinal haemangioblastomata also occur (Ramsey *et al.*, 1987; Neumann *et al.*, 1989). Hypernephroma of the kidney and phaeochromocytoma of the adrenal gland as well as pancreatic and epididymal cysts are also part of the syndrome, which is one of a group of conditions known as the phakomatoses (van der Hoeve, 1932).

Case report

A 24-year old Caucasian female presented with an eight year history of progressive hearing loss in the left ear and a three year history of progressive left-sided facial weakness resulting in a complete palsy which had not recovered. Over the previous 12 months she had suffered from left otalgia, transient episodic rotatory vertigo with nausea, occasional vomiting and generalized headaches.

Otoscopic examination revealed a pulsatile red mass in the middle ear, producing a bulging of the posterior half of the left tympanic membrane. Pure tone audiometry demonstrated a 'dead' ear on that side. She manifested a total or House grade VI facial palsy. Computerized tomography (CT) in the axial plane revealed extensive destruction of the petrous temporal bone (Fig. 1). A tympanotomy and biopsy of the mass was performed under general anaesthesia. Histological examination revealed a choroid plexus tumour.

At this stage the patient was referred to the Department of Otoneurosurgery at Addenbrooke's Hospital where, in addition, she was noted to be markedly unsteady on her feet. She was Romberg positive and very unsteady during Unterberger's stepping test. Ataxia, dysdiadochokinesis and past pointing were noted. Magnetic resonance imaging (MRI) demonstrated a large heterogeneous mass centred on the left temporal bone (Figs. 2a & b). It extended superiorly to the level of the upper pons and inferiorly to the arch of C1. Medially it compressed the cerebellum extra-axially and extended anteriorly to the middle cranial fossa, deforming the temporal lobe. Four vessel cerebral angiography showed that the tumour was mainly supplied by the ascending pharyngeal branch of the external carotid artery (Fig. 3). There was no contribution from the internal carotid artery.

Shortly after angiography the patient complained of blurred vision in the inferior peripheral field of her left eye. Examination of the fundi revealed bilateral retinal angiomata (Fig. 4). In the temporal retina of the right eye a large angioma was seen, surrounded by exudate, and a smaller angioma was in close proximity. Interestingly there was also a white lesion present in the left eye (Fig. 5) which appeared to be an angioma which had spontaneously regressed (Whitson *et al.*, 1986; Schmidt and Neumann, 1987). Bilateral retinal angiomatosis established a diagnosis of von Hippel-Lindau disease. Because of the known association of VHL and cerebellar haemangioblastoma, the histology of the brain tumour was reviewed (IF) and the diagnosis of choroid plexus tumour confirmed in this case. The neuroradiological findings were also not in favour of haemangioblastoma because the lesion was not axial and the blood supply came from the ascending pharyngeal branch of the external carotid artery and not from the posterior cerebral circulation, as would be expected for a cerebellar haemangioblastoma.

Surgery

The patient underwent a left temporal bone resection and a posterior translabyrinthine and anterior transcochlear approach was made to the cerebellopontine angle. The tumour was extensive and very vascular, but it was possible to define a plane of cleavage between it and the cerebellum, and to separate it from the tentorium cerebelli. The most difficult part of the dissection was the region of the jugular bulb and around the carotid artery and petrous apex. The IXth, Xth and XIth cranial nerves were intact at the end of the procedure. A blind sac closure of the external auditory canal was performed. Fat was used to obliterate the temporal bone defect and lyophilized dura to graft the defect. A lumbar drain was inserted for five days. The patient's recovery was uneventful.

A post-operative abdominal CT scan showed the presence of renal and pancreatic cysts (Fig. 6), which is consistent with the diagnosis of VHL disease.

Cryotherapy to the angiomata in the right eye, using the single

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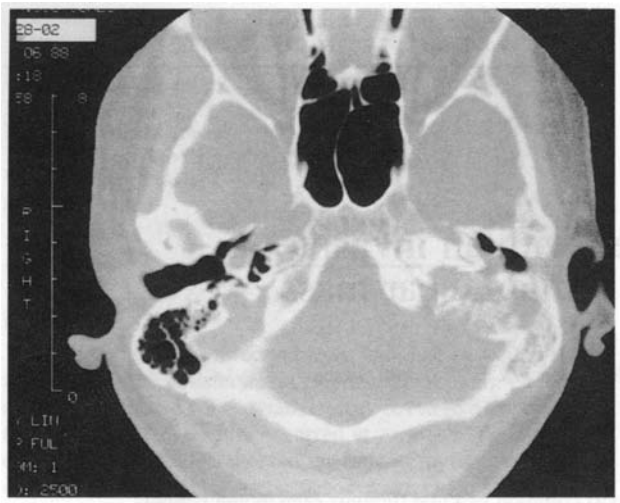


Fig. 1
CT of the brain in the axial plane.

freeze technique, was performed. This led to regression and scarring of the angioma.

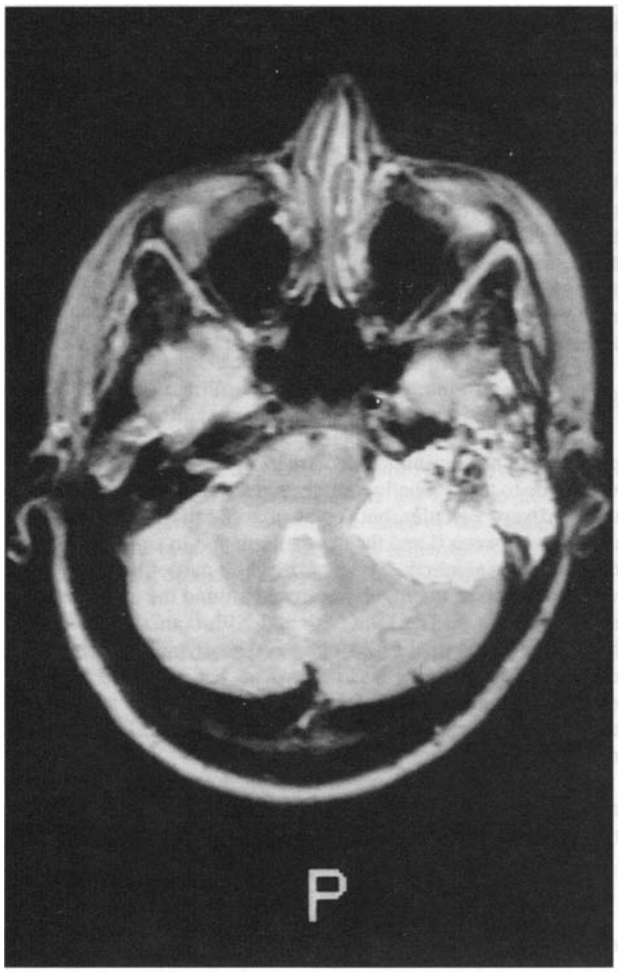
Pathology

The typical choroid plexus papilloma has a characteristic frond-like pattern and the papillae are lined by a single layer of well-differentiated cuboidal to columnar epithelium (Coffin *et al.*, 1986). The nuclei are round and occupy the basal portion of the cells which rest on a basal lamina. Pseudo-stratification and more solid foci may be found and also columnar secretory cells. The fibrovascular stroma of the papillary stalks may be hyalinized or myxomatous and is of presumed leptomeningeal origin. Histology on the original specimen showed a papillomatous tumour enveloped in the mucosa of the middle ear giving it a cystic appearance (Figs. 7 & 8). At higher magnification, the fibrovascular stalk was covered by a single layer of cuboidal to columnar cells (Fig. 9). The vascular stroma appeared to be hyalinized and myxoid. A choroid plexus tumour was diagnosed. Histology of the specimen obtained at craniotomy confirmed this.

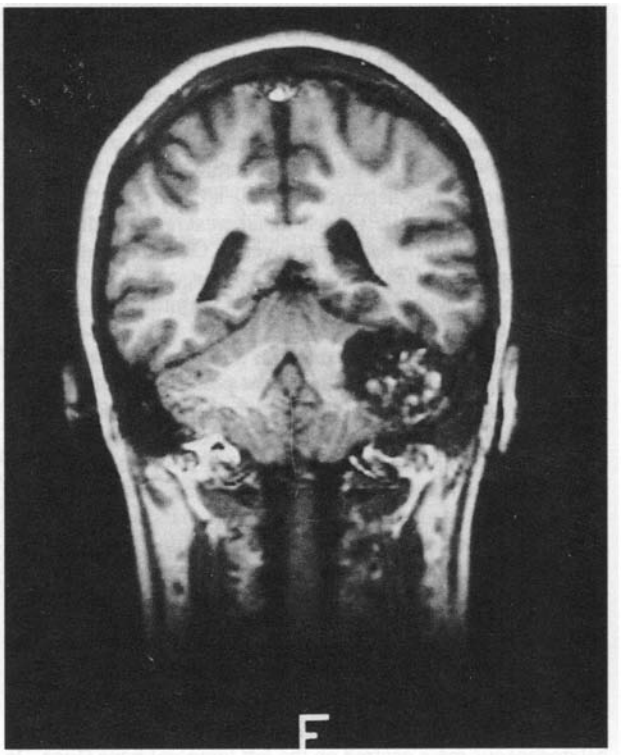
Microscopy of the craniotomy specimen showed the intertrabecular spaces of the temporal bone infiltrated by neoplastic tissue of papillary pattern (Fig. 10). The lining of cuboidal to columnar cells covering the vascular connective tissue core was moderately stratified and there was some irregularity of cellular and nuclear shape and size; there were no mitoses in either of the specimens examined. Glandular features were absent.

Immunochemical stains were used on the tissue and the cells stained positively with both epithelial cytokeratin (CAM 5.2) and glial fibrillary protein markers in both specimens (Coakham *et al.*, 1985; Cruz-Sanchez *et al.*, 1989). Neurone specific enolase (NSE) and S-100 protein gave positive results (Gaffey *et al.*, 1988; Heffner, 1989). Carcino-embryonic antigen was not detected and tests for laminin were inconclusive. These are consistent with a benign tumour of this type (Coakham *et al.*, 1985; Coffin *et al.*, 1986; Doglioni *et al.*, 1987; Cruz-Sanchez *et al.*, 1989) and assist in the differential diagnosis from adenomatous tumours.

Notwithstanding the lack of malignant features, such as cellular and nuclear pleomorphism, mitoses, focal necrosis and a loss of demarcation between stroma and parenchyma, the radio-



(a)



(b)

FIG. 2 (a & b)
MRI of the brain in the axial (a) and coronal (b) planes.

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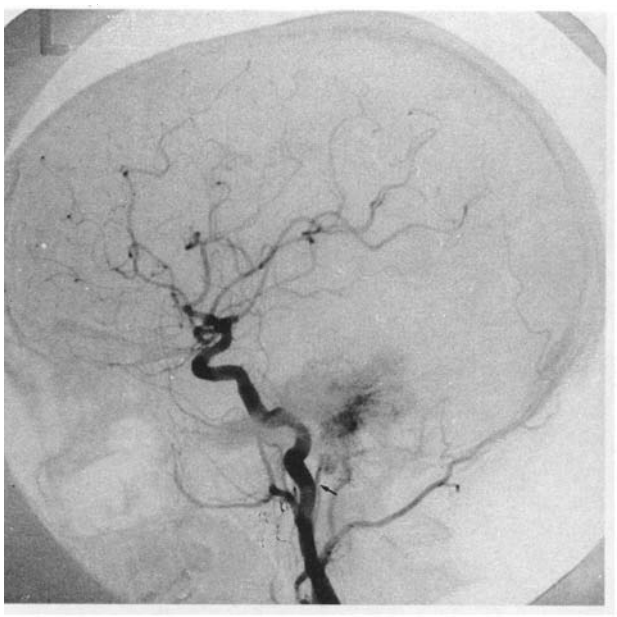

Fig. 3

Four vessel cerebral angiography. Black arrow points to ascending pharyngeal artery.

logical and surgical finding of extensive invasion of the petrous temporal bone were surprising and were those of a malignant tumour suggestive of a well-differentiated low-grade choroid plexus carcinoma.

Discussion

The diagnosis of von Hippel-Lindau disease is made in patients with more than one haemangioblastoma of the central nervous system or an isolated lesion in association with a visceral manifestation of the disease and in patients with only one feature if there is a known family history (Huson *et al.*, 1986).

Von Hippel-Lindau is an important disease to establish and undiagnosed lesions can lead to blindness or death. Sight-threatening retinal angiomata may be asymptomatic and careful fundoscopy is an important part of screening and should be performed annually (Goldberg and Duke, 1968; Goldberg and Koenig, 1974; Ridley *et al.*, 1986). Angiomata should be treated by

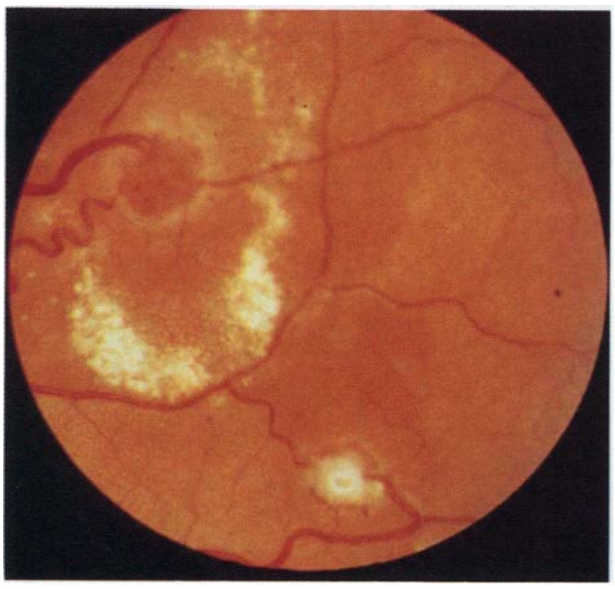

FIG. 4

Right fundus showing large angioma surrounded by exudate with smaller angioma nearby.

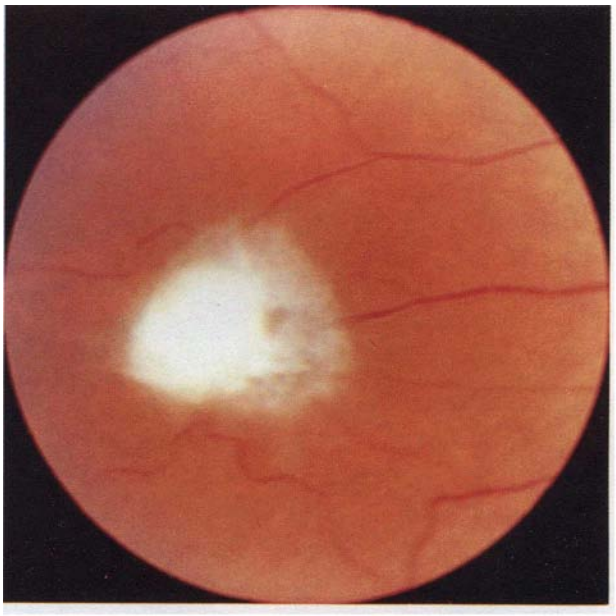

FIG. 5

Left fundus showing angioma which had spontaneously regressed.

cryotherapy or photocoagulation (Amoils and Smith, 1969; Welch, 1970; Watzke, 1973). Enhanced CT or MRI should be used to screen for cerebellar haemangioblastomata. Abdominal CT scan can demonstrate lesions of the kidney, adrenal and pancreas (Kuhlman *et al.*, 1987). Patients with VHL are at risk of developing multiple renal tumours and it is important to detect them at an early stage so that they can be treated by local excision (Malek *et al.*, 1987). Urinary vanillyl mandelic acid (VMA) and metadrenaline should be measured as a screen for phaeochromocytoma.

Genetic studies on patients with VHL show that it is inherited as an autosomal dominant with incomplete penetrance and genetic linkage studies have mapped theVHL disease gene to the tip of the short arm of chromosome 3 (King *et al.*, 1987; Zbar *et al.*, 1987; Decker *et al.*, 1988; Neumann *et al.*, 1988; Seizinger *et al.*, 1988). Sporadic cases do occur, presumably due to new mutations. There was no family history for our patient. The patient is an only child. The eyes of both parents were examined and found to be normal. Abdominal scans were also normal. Genetic coun-

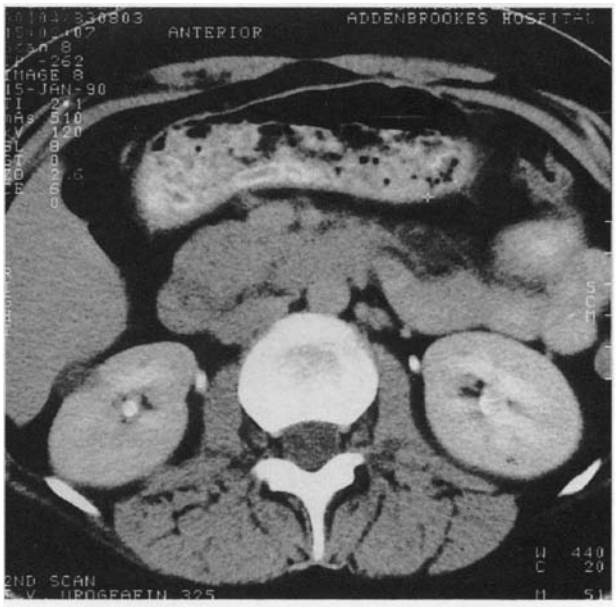

Fig. 6

Abdominal CT scan showing renal and pancreatic cysts.

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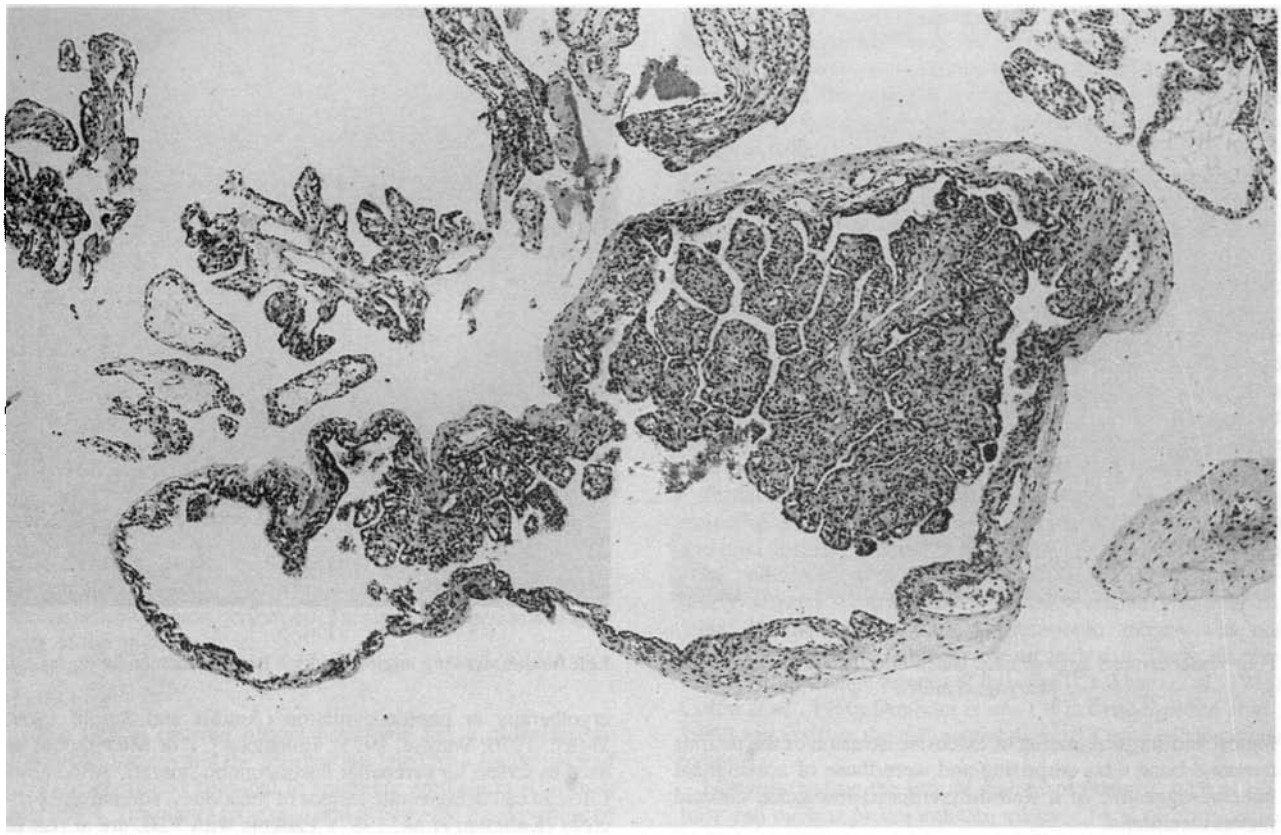

Fig. 7

Micrscopy shows a papillary tumour enclosed by the middle ear mucosa (biopsy specimen). Haematoxylin-eosin ×65.

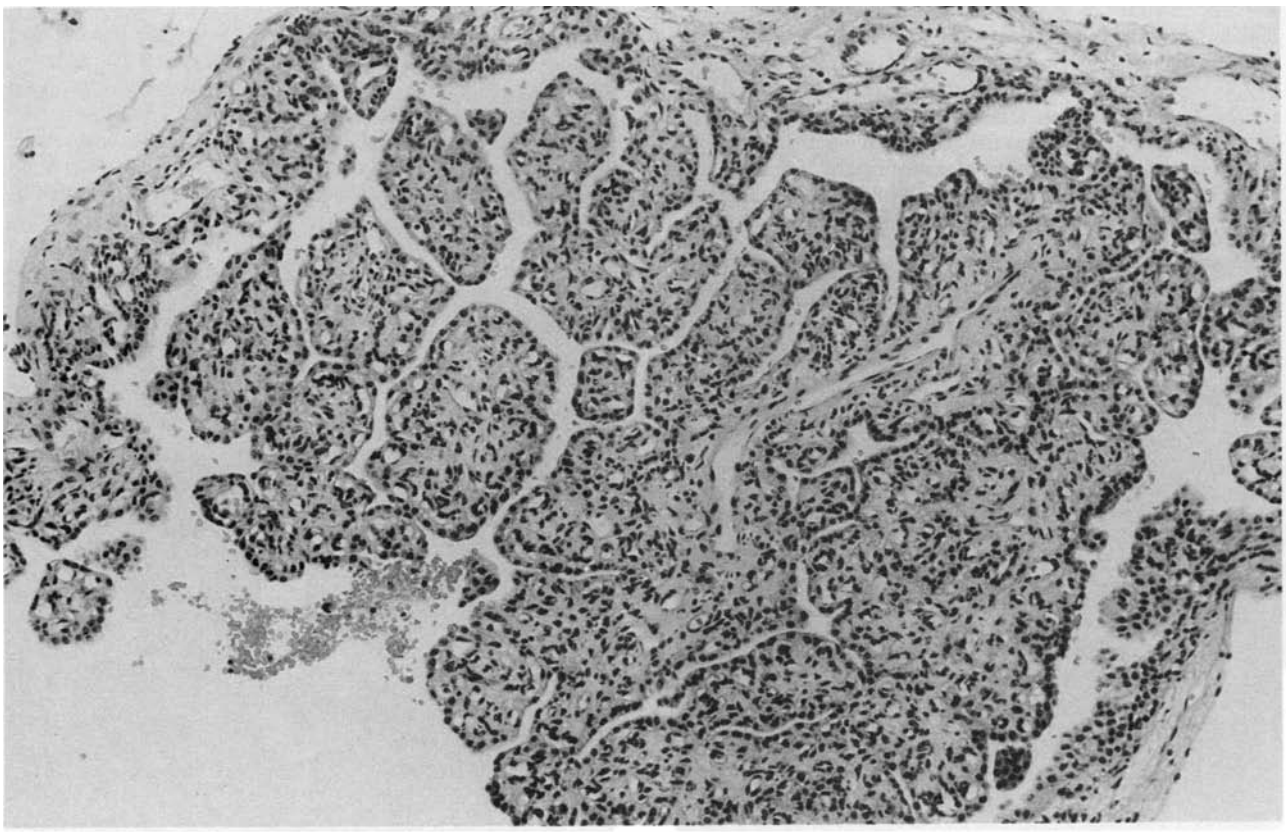

Fig. 8

To show, at higher magnification, the microscopical features of the tumour. The frond-like pattern is evident. Note fibrovascular papillary stalks covered by layer of cuboidal cells. Haematoxylin-eosin ×155.

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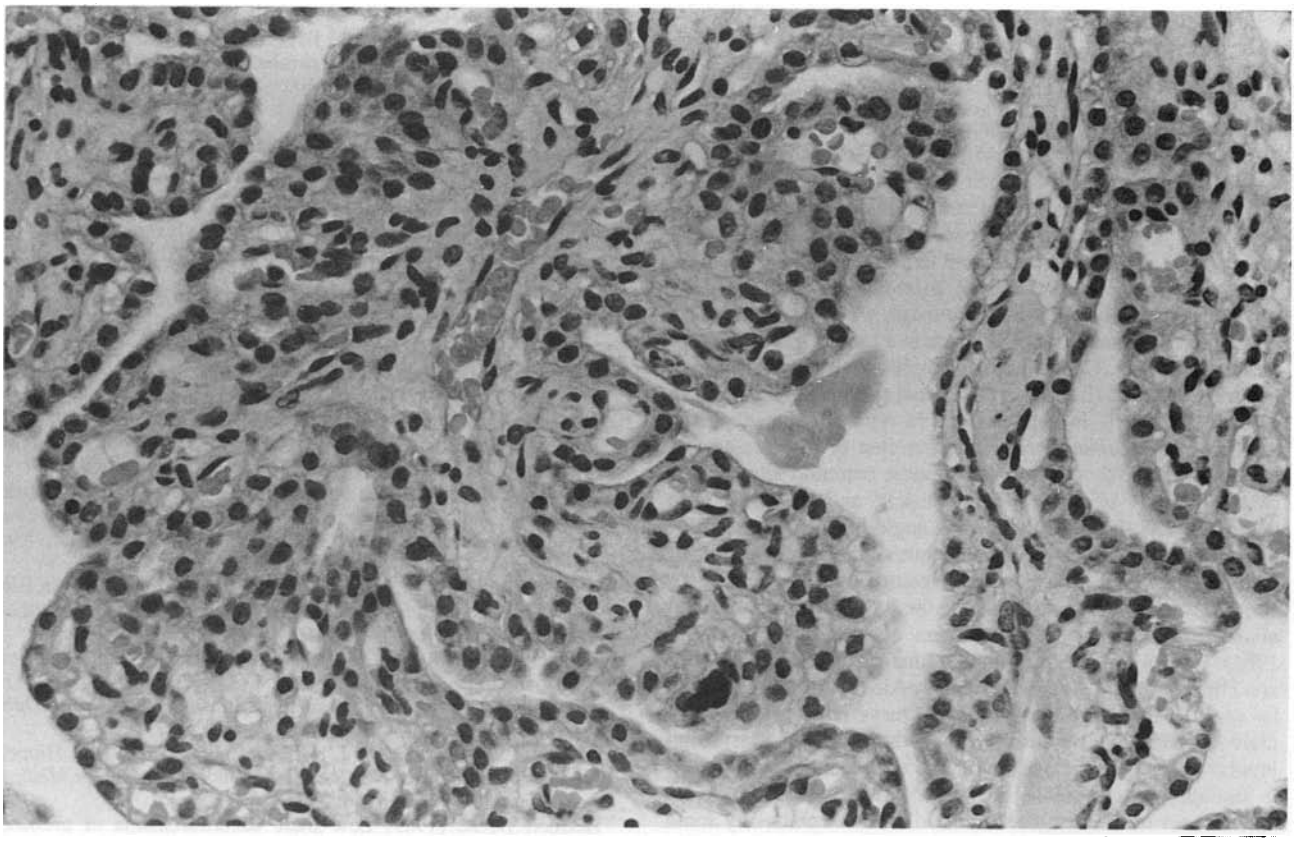

Fig. 9
Showing a papilla covered by taller cells. Note some irregularity of nuclear size and shape. Haematoxylin-eosin ×400.

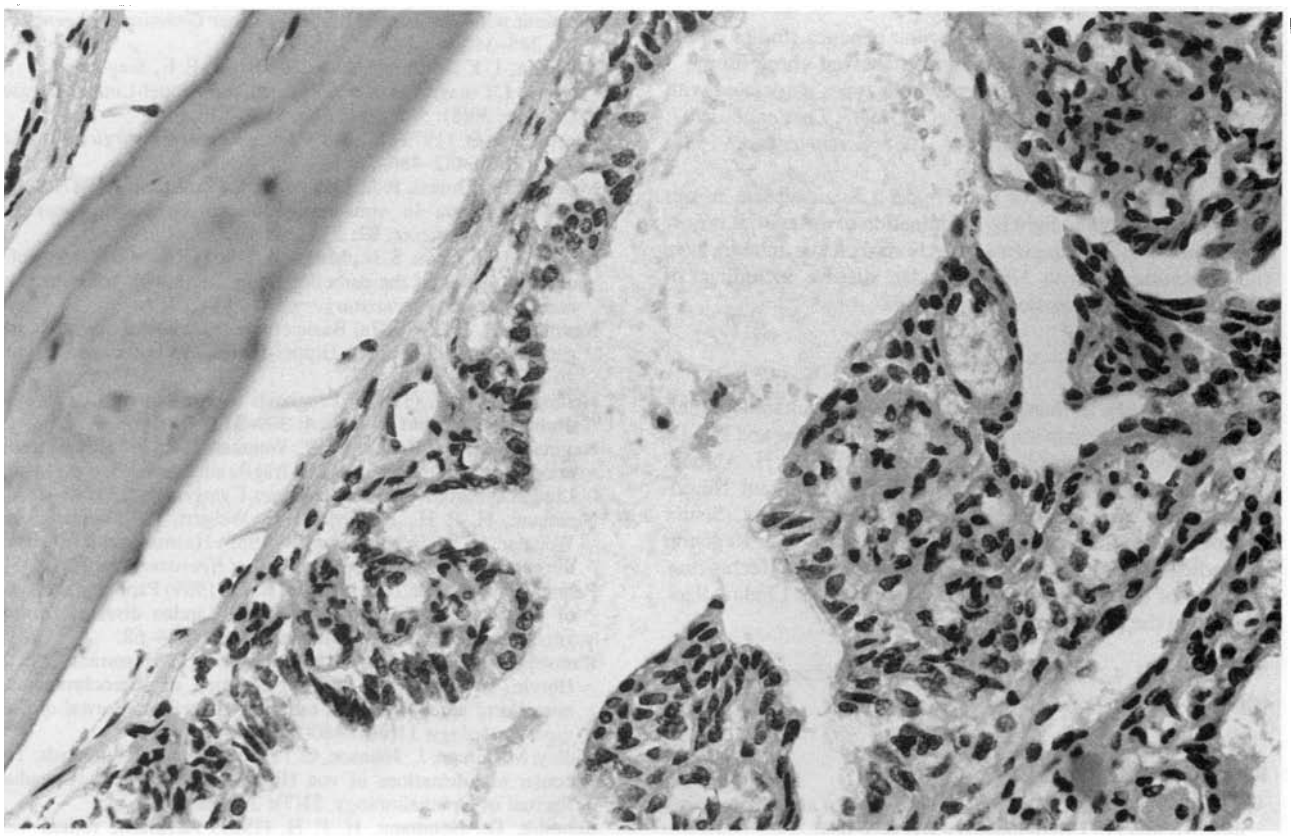

Fig. 10
Section of neoplastic tissue from the temporal bone showing a similar pattern.

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selling and screening of kindreds is important (Green *et al.*, 1986; Neumann, 1987a, b).

A reasonable screening routine is as follows: (Huson *et al.*, 1986).

Annual	(i)	Ophthalmoscopy from the age of five.
	(ii)	Urinary VMA and metadrenaline from the age of 10.
Biennial	(i)	Cranial CT from the age of 15 or if indicated or in the presence of symptoms suggesting an intracranial problem.
	(ii)	Abdominal CT from the age of 30.

This is the first case, to our knowledge, where a definite diagnosis of VHL disease has been made in a patient with a choroid plexus papilloma. Choroid plexus papilloma has been reported in a VHL kindred (Lauritsen, 1973) but there was no definitive evidence of VHL in that patient. In adults, choroid plexus tumours only account for 0.5–0.6 per cent of all intra-cranial tumours. The IVth ventricle is the most common site (50 per cent) followed by the lateral ventricle and then the IIIrd ventricle, with the cerebellopontine angle being the least common. Extensive involvement of the temporal bone with a pulsatile middle ear mass as a presenting feature is unique in itself for choroid plexus papilloma, let alone the previously unconfirmed association with von Hippel-Lindau disease (Naguib *et al.*, 1981). Choroid plexus papilloma alone or in association with von Hippel-Lindau disease should be added to the bottom of the list of causes of a pulsatile middle ear mass, below glomus jugulare tumours, aberrant intrapetrous internal carotid artery, high jugular bulb, adenoma and low grade adenocarcinoma.

Tumours with similar, if not identical histopathological appearances have been labelled middle ear adenomas by some authors (Gaffey *et al.*, 1988), and even low-grade adenocarcinomas of the endolymphatic sac origin (Heffner, 1989). These cases may well be other examples of choroid plexus neoplasms.

Palmer *et al.* (1989) described as adenoma a tumour resembling a choroid plexus tumour. It occurred in a patient with von Hippel-Lindau disease.

It is important to note that molecular genetics studies on the choroid plexus papilloma in our case showed chromosome 3 allele loss as described for other tumour types associated with von Hippel-Lindau disease (King *et al.*, 1987; Zbar *et al.*, 1987; Decker *et al.*, 1988; Neumann *et al.*, 1988; Seizinger *et al.*, 1988; Blamires and Maher, 1992).

Finally, the diagnosis of von Hippel-Lindau disease in our patient was brought to light by examination of the eyes. It is now very important that all patients with choroid plexus tumours have full screening for von Hippel-Lindau disease including, of course, dilated examination of the fundi.

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Figures 1, 3, 4, 5 and 6 are reproduced by kind permissin of the editor of *Eye*.

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