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Haemangioblastoma of a cervical sensory nerve root in Von Hippel-Lindau syndrome

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Abstract Spinal haemangioblastomas are rare, accounting for only about 7% of all central nervous system cases. The case of a 40-year-old woman with a haemangioblastoma arising solely from a cervical sensory nerve root is presented. At operation via a cervical laminectomy, it was possible to resect the tumour en masse with the sensory ramus, by extending the laminectomy through the exit foramen for C6. Haemangioblastomas are commonly intramedullary, and have only been re-

ported in this location on one previous occasion. The patient has Von Hippel-Lindau syndrome and a history of multiple solid tumours. The possible role of the Von Hippel-Lindau tumour suppressor gene in the pathogenesis of these neoplasms is discussed.

Key words Haemangioblastoma · Peripheral nerve root · Von Hippel-Lindau syndrome

Introduction

It was the German ophthalmologist Eugen Von Hippel (1867–1958) who, in 1904, first described the appearances of retinal angiomas. However, it was not until 1927 that the Swedish pathologist Arvid Lindau (1892–1952) made the connection between cerebellar tumours, renal tumours and the retinal disease. Our knowledge and understanding of Von Hippel-Lindau (VHL) syndrome has progressed considerably since this time, especially with the discovery of its gene in 1993 [16]. Subsequent work has further established this locus as an important site of tumour suppression. We know that spinal haemangioblastomas account for only about 7% of all central nervous system (CNS) cases [21], nearly all occurring in VHL syndrome. Spinal haemangioblastomas are almost exclusively intramedullary lesions, and it is only on extremely rare occasions that they have been reported outside this site.

Case report

A 40-year-old woman presented with a progressive history of neck and right arm pain associated with tingling and numbness in the right thumb and the sole of the right foot. Neurological examination revealed loss of light touch and pinprick sensation in the right thumb and a diminished supinator reflex. In the right leg there was increased tone, ankle clonus, brisk tendon reflexes and an upgoing plantar reflex. There was loss of vibration and joint position sense in the right foot and ankle. There were no positive cerebellar signs and fundoscopy was normal. On questioning, the patient had an extensive past medical history. In 1982 a melanoma was resected from the right thigh. In 1989 a pheochromocytoma was resected from the right adrenal. During this time she had multiple adenomata removed from both breasts, and in 1996 was diagnosed with a prolactin producing microadenoma of the pituitary gland. There was no relevant family history of note.

Magnetic resonance imaging (MRI) investigation of the cranio-spinal axis revealed numerous enhancing masses within the brain stem and spinal cord (Fig. 1). The largest lesions appeared both intradural and intramedullary at the levels of C5 and T1/2. There was an extensive syrinx, which spanned the whole length of the spinal cord. Abdominal ultrasound examination revealed multiple benign cysts of both kidneys. The haemoglobin and haematocrit concentrations were within normal limits.

At operation, to aid decompression of the syrinx and prevent complications related to the brain stem lesions, a foramen magnum decompression was first undertaken. In addition, a C4–6 cervical

Fig.1 A T1-weighted sagittal magnetic resonance (MR) image with gadolinium of the spinal axis. Multiple enhancing lesions are demonstrated, the largest at C5 and T1/2. There is an extensive syrinx throughout the spinal cord and lower brain stem. B T1-weighted axial MR image through C5/6 showing the enhancing lesion compressing the spinal cord and extending laterally on the right side through the C6 exit foramen. The lesion can be seen to be in close proximity to the posterior aspect of the vertebral artery

Fig.2 Operative photograph following resection of the tumour. The dura has been opened between C4 and C6. The cord has obviously been distorted by the tumour, but not invaded (*black arrows*). Abnormally dilated blood vessels can be seen on the cord surface

laminectomy was performed. On opening the dura at C4-6 and decompressing the syrinx, to our surprise the tumour was seen to arise entirely from the posterior sensory branch of C6. It was possible to dissect the tumour via a plane of cleavage from the cord and resect the tumour en masse with the sensory ramus by extending the laminectomy through the exit foramen for C6 (Fig.2). The patient recovered uneventfully from surgery and was discharged 7 days later. On clinical review 6 months later, the patient was fully mobile, and showed improvement in long tract signs and resolution of right arm pain. The area of C6 sensory loss, however, was more extensive.

Histology of the tumour revealed it to be a haemangioblastoma, and subsequent genetic testing of the patient has shown her to carry the gene for Von Hippel-Lindau syndrome.

Discussion

Haemangioblastoma is a benign, highly vascular tumour limited almost exclusively to the central nervous system

[9]. Spinal haemangioblastomas are rare tumours accounting for less than 2% of all spinal cord tumours [4,19] and 7% of haemangioblastomas [21]. They most commonly present with symptoms of spinal cord compression, radicular pain or symptoms related to an associated syrinx [12]. Rarely, spinal cord haemangioblastoma can present with subarachnoid haemorrhage [8]. They are intramedullary tumours and are said to arise most commonly in the posterior columns of the spinal cord, or extend from the pia on the posterior surface of the cord into the posterior columns [20]. Only in extremely rare instances have they been reported in an intradural, extramedullary site [20], and we could find only a single report in the English literature of a haemangioblastoma arising from an intradural cervical nerve root [7], as described in this case. They have, however, been described in the filum terminale [19], and there are two reports of haemangioblastomas arising on peripheral nerves: the radial nerve [2] and the sciatic nerve [7]. These cases support the hypothesis that haemangioblastomas are not derived from astrocytes.

The association of haemangioblastoma with VHL syndrome is said to occur in 20–30% of cases [19,20]. Von Hippel-Lindau syndrome is an autosomal dominant disorder, predisposing to the development of various tumours (CNS and retinal haemangioblastomas, endolymphatic sac (ELS) tumours, renal cell carcinoma and/or renal cysts, pheochromocytomas, pancreatic cysts and/or tumours). The incidence of the disease is 1/36,000. Central nervous system haemangioblastomas and renal cell carcinoma are the main causes of death.

The VHL gene located on chromosome 3p25–26, is a tumour suppressor gene encoding for a 213 amino acid protein, which plays a major role in regulation of vascular endothelial growth factor (VEGF) expression. This amino acid has a direct effect on the rate of transcription in many cells, and allows the gene to aid tumour suppression.

What is interesting about the case presented is that, as well as the unusual site of the haemangioblastoma, there are the multiple tumour pathologies. The incidence of pituitary adenoma in cases of VHL syndrome is 0.5% [15], which is higher than that in the general population (reported as 0.02% [6]). The VHL protein has been identified in the eosinophilic cells of the pituitary gland as well as in the normal sites of the disease (neural cells, renal tissue and adrenal cortex) [11]. There is no reported connection between malignant melanoma or breast papilloma and VHL syndrome. It is interesting to speculate about the role of the VHL tumour suppressor gene in these processes.

Another interesting aspect to the case is the presence of two endocrine tumours. The patient had a pituitary adenoma, often part of the multiple endocrine neoplasia (MEN) syndrome type 1, and a pheochromocytoma, which is part of the MEN syndromes type 2a and 2b. The distinction between these endocrine syndromes has been

questioned by some authors who believe the tumours should be considered to exist in combination and not as separate syndromes [1].

The origin of haemangioblastomas has not been clearly delineated, but recent research indicates that VEGF secreted from the stromal cells plays an important role in endothelial cell proliferation [10,14]. Haemangioblastomas overexpress the hypoxia-inducible gene VEGF as a consequence of mutational inactivation of the VHL tumour suppressor gene [10]. Hypoxia-inducible factor-1 activation may underlie the angiogenic phenotype of VHL-associated tumours [13].

Spinal cord haemangioblastomas in VHL disease are often multiple and located at various sites. Surveillance should start in childhood and requires annual follow-up with MR imaging of the CNS.

Complete excision is imperative to prevent recurrence and a high index of suspicion is necessary to make a pre-operative diagnosis. Radical excision of haemangioblastomas can be achieved at low levels of surgical mortality

and morbidity [18]. Symptomatic patients should undergo surgery before they develop extensive sensorimotor deficits. In patients with multiple lesions, tumours distant from the symptomatic one should not be tackled [5]. Haemangioblastomas are highly vascular tumours, often accompanied by enlarged feeding and draining vessels. Although haemorrhage is a distinct danger, care must be taken to avoid indiscriminate cautery of these vessels, as they may be important in preventing spinal cord ischaemia.

In recent times a role for stereotactic radiosurgery has been suggested for tumours in surgically inaccessible locations or multiple tumours such as in VHL disease [3].

In conclusion we present a case of spinal haemangioblastoma in a very unusual location in a patient with many possibly interconnected tumour pathologies. For neurosurgeons the search for VHL disease is imperative in cases of an apparently 'sporadic' CNS haemangioblastoma or ELS tumour [17].

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