SHORT REPORT

A case of multiple cutaneous schwannomas; schwannomatosis or neurofibromatosis type 2?

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A 54 year old man presented with numerous cutaneous schwannomas, cranial nerve lesions, and spinal cord lesions, but no evidence of vestibular nerve involvement. There was no family history of neurocutaneous lesions. To help discriminate between the various possible diagnoses in this patient, molecular analysis of two cutaneous schwannomas was undertaken. An identical point mutation in the NF2 gene in the two anatomically distinct tumours was found, confirming this as a case of NF2 mosaicism.

The term “schwannomatosis” has been used to describe a phenotype of multiple cutaneous schwannomas in the absence of bilateral vestibular schwannomas. Although schwannomatosis is regarded by some as a distinct phenotype,^{1–3} there is some overlap with neurofibromatosis type 2 (NF2), making it difficult to distinguish between these two diagnoses on clinical grounds. A further complication is that the histological appearances of schwannomas from cases of schwannomatosis and NF2 are morphologically similar.⁴ Molecular analysis of the NF2 gene in patients with the schwannomatosis phenotype has demonstrated frameshift, nonsense, and truncating mutations in the tumour tissues,^{5–6} but no evidence of germline mutations as found in cases of NF2.

CASE REPORT

A 54 year old man was referred to the neurology clinic. He had acquired a diagnosis of neurofibromatosis type 1 (NF1) about 20 years earlier after some painful lumps were removed from his right hand and found to be schwannomas. The lumps recurred and further lesions had gradually developed on his back, left arm and hand, left leg, trunk, and face. There was no history of similar lesions in his parents, siblings, or three children.

At the time of presentation he complained of a 15 year history of episodic altered sensation in his legs, worse on the left than the right. He described a feeling of heat radiating from his waist to his knees, associated with numbness of his left leg, lasting about five minutes before gradually resolving from the knees up. Walking even relatively short distances precipitated pain in his left hip, which radiated to his knee and would last anything from hours to several days. Occasionally he would feel unsteady on his legs and he had a tendency to lean to one side. He experienced excruciating pain whenever the lumps were touched, and in the upper limbs the pain was often associated with numbness, lasting for several minutes or hours.

On examination he had multiple cutaneous lesions in the upper limbs, trunk, back, left leg, and face, all of which were painful when touched. The largest, in his left palm, was the size of an egg and was particularly tender (fig 1). There were no abnormal neurological signs on examination of the head

and neck. Examination of the upper limbs was limited by pain but the range of movement was preserved. Tone was normal and there was no focal weakness. In the lower limbs there was some subtle wasting of the left thigh and definite weakness of hip flexion on the left. Reflexes were preserved and both plantar responses were flexor. There was no reproducible focal sensory loss but there was a subjective reduction in sensation to pinprick and temperature over the whole of the left side of his body, including the face, but not the tongue or the inside of the mouth.

The cutaneous lesions were not typical in appearance or distribution for neurofibromatosis type 1 and there were no café au lait patches, axillary freckling, or obvious Lisch nodules. Histological review of the lesions that had been removed previously confirmed that they were typical schwannomas with frequent Verocay bodies. The tumour cells stained positively with anti-S100. The most appropriate diagnosis was thought to be schwannomatosis.

A formal ophthalmological assessment did not identify any ocular changes consistent with NF1 or NF2, although a few small dot cortical lens opacities were present peripherally. His hearing was felt to be within normal limits for his age, and auditory brain stem response testing was essentially normal. Magnetic resonance imaging (MRI) of the brain showed an extra-axial mass lesion arising around the left pre-pontine cistern superior to the internal auditory meati, which distorted the left side of the pons and left middle cerebral

Figure 1 Cutaneous schwannomas on the left palm and dorsal aspects of both hands. Patient consent was obtained for publication of this figure.

Figure 2 Axial magnetic resonance imaging through the posterior fossa post-contrast showing an enhancing mass lesion in the left cerebellopontine angle, distorting the left side of the pons.

peduncle and extended forward into Meckel's cave. It was interpreted as being consistent with a nerve sheath tumour of the trigeminal nerve (fig 2).

MRI of the spine showed multiple abnormalities (fig 3). Serpiginous low signal areas were seen over the surface of the cord and within the dura from the upper thoracic region to the lower lumbar region, suggesting a spinal vascular malformation. This was supported by the enhancement of the surface of the cord following intravenous contrast. There were also several discrete mass lesions, the largest of which lay within and distended the sacral thecal sac, distorting and eroding adjacent sacral vertebral bodies. A smaller mass lesion was visible at T9/10 anteriorly, lying extradurally on the right side of the dural tube. The masses were assumed to be schwannomas and the signal and contrast enhancement characteristics were consistent with this.

Two and a half years after his initial referral, his symptoms had not progressed significantly. There was a mild global weakness of the left leg, with depressed knee and ankle jerks on that side, and a mild impairment of soft touch and pin prick over his left face, arm, and leg. He underwent surgical removal of two lesions on the left hand, one from the palm and one from the dorsal aspect of the left forefinger. Histological examination again showed the appearances of schwannomas with frequent Verocay body formation.

GENETIC STUDIES

Molecular analysis of the NF1 gene by denaturing high performance liquid chromatography (DHPLC), using DNA from peripheral lymphocytes, did not reveal a mutation. Fluorescence in situ hybridisation (FISH) studies—using the probes P1-9 and P1-12, which map to the NF1 gene region at 17q11.2—showed no evidence of a deletion in that region. Analysis of the NF2 gene by direct sequence analysis was normal. Tissue from the two lesions was frozen and DNA was extracted. Separate DNA samples were forwarded to the National Genetics Reference Laboratory in Manchester for further analysis of the NF2 gene. Although no mutation had previously been detected in the patient's lymphocytic DNA, a point mutation in exon 1, K20X (nt 58A→T), was found independently in both tumour DNA samples and a

Figure 3 Sagittal T2 magnetic resonance image through the lower spine showing abnormal serpiginous vessels around the conus and inferior thecal sac. There is also a large hyperintense mass lesion eroding the posterior aspect of the sacrum.

heterozygous deletion of exons 1, 4, 8, and 15 was detected by dosage polymerase chain reaction in the first tumour DNA sample. In addition, loss of heterozygosity (LOH) analysis of the first tumour sample using the closely linked microsatellite markers D22S275 and NF2CA3 showed LOH with both markers consistent with the observation of a deletion on dosage analysis. This demonstration of two identical point mutations in separate tumours confirmed a diagnosis of mosaic NF2.

DISCUSSION

Schwannomas are benign peripheral nerve sheath tumours that can occur in isolation or as part of neurofibromatosis type 2, when they typically involve the vestibular nerves bilaterally. Cutaneous schwannomas may easily be confused with neurofibromas, which are a feature of neurofibromatosis type 1. However, it is important to distinguish between them as persistent pain in a subcutaneous neurofibroma is unusual and might be suggestive of malignant change. Cutaneous schwannomas, however, are characteristically tender, often causing shooting pain and dysaesthesia after even trivial trauma. The histological appearances of schwannomas in schwannomatosis and NF2 are similar, with frequent Verocay bodies and a lobular, "grape-like" architecture, a pattern which is uncommon in sporadic schwannomas.^{4,7}

The presence of multiple cutaneous schwannomas without vestibular nerve involvement has been termed schwannomatosis. However, making the distinction between schwannomatosis and NF2 on clinical grounds alone can be difficult. Early reports of the condition, before the NIH consensus statement on NF2,⁸ seem to have included several patients who would now be classed as having NF2. However the exact

frequency of NF2 in those patients described as having schwannomatosis is impossible to ascertain as many of them did not undergo cranial imaging.

In this case there are some phenotypic similarities with typical NF2. Apart from bilateral vestibular schwannomas, NF2 is associated with meningiomas, intramedullary and cauda equina gliomas, and schwannomas of the 12th, eighth, and fifth cranial nerves.⁷ Although the exact identity of the extra-axial mass arising from the fifth cranial nerve in this case is not known it would be consistent with a schwannoma. The combination of intracranial lesions and a vascular malformation of the spinal cord has not previously been reported in a case of schwannomatosis, and as so few schwannomatosis patients have had extensive neuro-axis imaging, it is not possible to be certain whether the vascular appearances are a coincidental finding or a part of the pathological process. However, it does seem likely that the combination of cutaneous, cranial nerve, and spinal schwannomas and the arteriovenous malformation would account for the neurological symptoms and deficit in this case.

As mutation analysis of the tumours from patients with schwannomatosis is not routinely undertaken, the exact role of the NF2 gene in the aetiology of the condition remains unclear. Examination of tumours from schwannomatosis patients has shown frequent truncating mutations of the NF2 gene and loss of heterozygosity of the surrounding region.⁵ Some patients can be shown to be somatic mosaics for NF2 mutations, as demonstrated by the presence of identical mutations in more than one tumour.

The prevalence of mosaicism in NF2 is unknown, although two recent studies have given estimates of 24.8% and 30%.^{9, 10} In some cases the mosaicism was apparent from the low level of the mutant allele on SSCP/heteroduplex analysis of lymphocyte DNA. In others, no mutation was detected in lymphocyte DNA but analysis of tumour DNA revealed mutations which were confirmed to be constitutional, either by the presence of the same mutation in an anatomically distinct second tumour or by the demonstration of allelic loss of the NF2 gene in addition to the mutation in a single tumour.

It was initially suggested that somatic NF2 mosaics may have up to a 50% risk of passing the NF2 mutation on to their offspring.¹¹ However, this risk now appears to be very low. A recent study reported that there have been no cases of NF2 among the offspring of patients who, like ours, have a point mutation in multiple tumours but not in blood.¹⁰ Thus,

although tumour analysis may not always be appropriate or possible, in this case it has enabled us to give our patient a definitive diagnosis and some reassurance about the risks to his children and grandchildren.

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REFERENCES

- 1 **MacCollin M**, Woodfin W, Kronn D, *et al.* Schwannomatosis: a clinical and pathological study. *Neurology* 1996;**46**:1072-9.
- 2 **Shishiba T**, Niimura M, Ohtsuka F, *et al.* Multiple cutaneous neurilemmomas as a skin manifestation of neurilemmomatosis. *J Am Acad Dermatol* 1984;**10**:744-54.
- 3 **Purcell SM**, Dixon SL. Schwannomatosis. An unusual variant of neurofibromatosis or a distinct clinical entity? *Arch Dermatol* 1989;**125**:390-3.
- 4 **Seppala MT**, Sainio MA, Haltia MJ, *et al.* Multiple schwannomas: schwannomatosis or neurofibromatosis type 2? *J Neurosurg* 1998;**89**:36-41.
- 5 **Jacoby LB**, Jones D, Davis K, *et al.* Molecular analysis of the NF2 tumor-suppressor gene in schwannomatosis. *Am J Hum Genet* 1997;**61**:1293-302.
- 6 **Kaufman DL**, Heinrich BS, Willet C, *et al.* Somatic instability of the NF2 gene in schwannomatosis. *Arch Neurol* 2003;**60**:1317-20.
- 7 **Louis DN**, Ramesh V, Gusella JF. Neuropathology and molecular genetics of neurofibromatosis 2 and related tumours. *Brain Pathol* 1995;**5**:163-72.
- 8 **National Institutes of Health**. Consensus Development Conference statement on neurofibromatosis. *Neurofibromatosis Research Letter* 1987;**3**:3-6.
- 9 **Kluwe L**, Mautner V, Heinrich B, *et al.* Molecular study of frequency of mosaicism in neurofibromatosis 2 patients with bilateral vestibular schwannomas. *J Med Genet* 2003;**40**:109-14.
- 10 **Moyhuddin A**, Baser ME, Watson C, *et al.* Somatic mosaicism in neurofibromatosis 2: prevalence and risk of disease transmission to offspring. *J Med Genet* 2003;**40**:459-63.
- 11 **Evans DGR**, Mason S, Huson SM, *et al.* Spinal and cutaneous schwannomatosis is a variant form of type 2 neurofibromatosis: a clinical and molecular study. *J Neurol Neurosurg Psychiatry* 1997;**62**:361-6.