CLINICAL AND PATHOLOGICAL ASPECTS OF SOLITARY SPINAL NEUROFIBROMA

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Four cases are described of solitary spinal neurofibroma, a rare tumour of the spinal cord or nerve roots. Computerised tomography provided an accurate topographical definition of the tumour. Magnetic resonance imaging showed an increased T2-weighted signal and multiple areas of decreased T1- and T2-weighted signals centrally. The MR signals matched the histological examination which showed hyperplastic interfascicular connective tissue, pleomorphic cells, and tightly packed nerve fibres compressed by the surrounding loose connective tissue. Electron microscopy showed three types of cell: Schwann cells, fibroblast-like cells, and mast cells. The histological findings suggests that solitary spinal neurofibroma is a distinct pathological entity which could be diagnosed preoperatively from the MR images.

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Spinal neurofibroma is one of the rarest of the neoplasms involving the spinal cord or roots and occurs much less often than neurinoma, meningioma or glioma (Minckler 1971; Hertzog et al 1980; Enzinger and Weiss 1983; Harkin 1986). It is now recognised, although not universally, as an entity distinct from the more common spinal neurinoma (Sanguinetti, de Santis and Rosa 1981).

The first systematic classification of nerve tumours was that of von Recklinghausen (1882) in the context of phakomatosis, a disorder characterised by disseminated hamartomas of the eye, skin and brain. He introduced the term 'neurofibroma', attributing the histogenesis of this tumour to the endoneurial and perineurial sheaths. Subsequently, all similar lesions, not necessarily related to von Recklinghausen's disease, were grouped under the one term.

In the past many authors have considered neurinoma and neurofibroma to be the same (von Recklinghausen 1882; Adair and McLean 1937; Zülch 1965; Nittner 1976) while others maintained the distinction between them (Verocay 1910; Lhermitte and Leroux 1923; Penfield and Young 1930; Tarlov 1940; Stout 1958; Masson 1968; Catalano, Fanfani and Mazzone 1985; Russell and Rubinstein 1989). There is also controversy as to the cells from which these lesions originate and from these uncertainties there have arisen such terms as schwannoma, peripheral glioma, perineurial fibroblastoma, neurilemmoma, etc (Poirier, Escourolle and Castaigne 1968).

The clinical data and the imaging and macroscopic appearances are rarely sufficient to differentiate between neurinoma and neurofibroma but taking account of the specific histological and ultrastructural differences, most authors now prefer to distinguish between them (Minckler 1971; Enzinger and Weiss 1983; Chomette et al 1984; Okazaki and Scheithauer 1988; Halliday, Sobel and Martuza 1991; Sanguinetti et al 1991). In agreement with others (Erlandson and Woodruff 1982; Bouldin 1990), we define spinal neurofibroma as a primary, commonly benign tumour of the spinal cord or nerve roots, which is pathologically different from spinal neurinoma and may be single or multiple.

The current tendency is to separate the single from the multiple lesions, since the latter are related to type 1 von Recklinghausen's disease, just as multiple neurino-

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mas are related to type 2 von Recklinghausen's disease (Halliday et al 1991). Both single and multiple lesions may occur without other stigmata of neurofibromatosis (Bouldin 1990), but what may appear to be a solitary spinal neurofibroma may be a prodromic lesion of neurofibromatosis (Minckler 1971; Riccardi 1982), particularly in young patients (Sbrocca, Gorini and Artesi 1989).

Solitary spinal neurofibroma is thus a rare tumour which is difficult to classify and to diagnose. We studied four patients with solitary spinal neurofibroma to gain some insight into the diagnostic and therapeutic problems of this tumour and to identify its clinical and pathological characteristics.

PATIENTS AND METHODS

We studied three men and one woman with a mean age of 41.5 years. The signs and symptoms of neurofibromatosis had been excluded by the history and by examination.

The duration of symptoms and the neurological signs before surgery were recorded. In all patients anteroposterior and lateral radiographs of the spine were obtained; myelography was performed in three patients, CT in three, and MRI in three. Table I shows the clinical details.

Histology and ultrastructure. Pathological tissue from all four tumours was fixed in 4% formaldehyde in 0.1 M phosphate buffer, pH 7.4, at 4°C for 24 hours. One half of each specimen was washed in tap water, dehydrated in graded alcohols, cleared in chloroform, embedded in paraffin, cut transversally and longitudinally into thin sections of 5 to 6 µm and stained with haematoxylin and eosin and Masson's trichrome stain. Bielschowsky's method was used for nerve fibres, Gomori and Fulmer stains for fibres and reticulum, and alcian blue for glycosaminoglycans.

The other half of each specimen was fixed in 4% formaldehyde in 0.1 M phosphate buffer, pH 7.4, at 4°C for 12 hours, then sectioned into 1 mm cubes with a stereomicroscope. These were postfixed in 1.3% osmium tetroxide, pH 7.4, in Molloig's buffer for one hour, dehydrated first in graded concentrations of ethanol and then in propylene oxide and embedded in Agar 100

epoxide resin (Agar Scientific, Stanstead, UK). Ultrathin (80 to 90 nm) sections obtained with a diamond-blade ultramicrotome (Ultratome III, LKB, Bromma, Sweden) were mounted on copper grids, stained with lead citrate and uranyl acetate and examined by a transmission electron microscope (Philips EM 400, Philips, Eindhoven, The Netherlands).

RESULTS

Clinical findings. The first symptom was always vertebral pain with or without radicular pain. Motor deficiency due to nerve root compression was seen in the two patients with lumbar lesions. At follow-up one patient had slight persistent weakness of the extensor digitorum communis of the foot.

Radiographic findings. Radiographic examination of three patients showed evidence of slow compression of the skeletal structures by the expanding lesion. These changes included erosion of the pedicles, increase in the interpedicular distance, distortion of the laminae, enlargement of a neural foramen and localised erosion of the vertebral body. In one tumour of the lumbar spine, the radiographs were negative.

Myelography. There were invariably secondary signs of the presence of the lesion. In two patients there was a characteristic block (Fig. 1), and in one a filling defect with 'amputation' of the root due to intraforaminal spread.

Computerised tomography. The images precisely defined the boundaries of the lesion and the extent of bone erosion and distinguished the typical hour-glass appearance of a tumour with intra- and extraspinal growth (Fig. 2).

Magnetic resonance imaging. On T1-weighted images the neoplasm showed intensity signals which were slightly higher than those of muscle. There was always an increased T2-weighted signal but with many areas of decreased signal intensity centrally. After injection of gadolinium DTPA contrast, the tumours showed a bright peripheral enhancement and non-uniform contrast enhancement in central areas (Fig. 3).

Surgical treatment. In all patients we performed laminectomy and opening of the dura to expose the neoplasm completely. Unlike neurinoma, spinal neurofibroma

Table I. Details of four patients with solitary spinal neurofibroma

Case	Age (yr)	Sex	History (mth)	Level	Site	Disturbances			Radiography	Myelography	CT	MRI	Follow-up (mth)
						Pain*	Motor	Sensory					
1	50	M	7	D12	Intradural	+	-	-	+	+	+	+	36
2	42	M	3	L4	Intra/extradural	+	+	+	+	+	+	+	15
3	35	M	4	L5	Intradural	+	+	+	-	+	-	+	31
4	39	F	9	C6	Intradural	+	-	+	+	-	+	-	59

*+, yes; -, no

lacks a well-defined capsule and since there is no easily identified cleavage plane careful dissection was necessary to avoid damage to the nerve roots and the radicular artery. The dura was meticulously repaired (Fig. 4).

Macroscopic examination. The tumour was solid, oval in shape and yellowish-brown in colour. It was softer and more elastic than a neurinoma which has a hard rubbery consistency. Fibres of the nerve roots involved lay almost always within the neoplastic parenchyma; by contrast the neurinoma displaces the root without involving it.

Histological examination. Hyperplasia of the interfascicular connective tissue was found in all cases (Fig. 5a). The matrix was rich in proteoglycans and there were numerous tightly packed collagen and reticular fibres. Stenosis was present in the fascicles, which were compressed by the surrounding connective tissue. There was no well-defined capsule. Numerous areas of myxoid degeneration were seen in the proliferating connective tissue and there was hyperplasia of the vascular stroma (Fig. 5b). The predominant cells were elongated with

Fig. 1a

Fig. 1b

Anteroposterior (a) and lateral (b) myelograms showing the secondary signs of a solitary lumbar neurofibroma. The characteristic block suggests intradural and extramedullary tumour growth (case 2).

Fig. 2a

Fig. 2b

Figure 2a – The axial CT image shows widening of the left L3-L4 intervertebral foramen, which is filled by a homogeneous soft-tissue mass. The lesion is slightly higher in attenuation values than the dural sac and the paraspinal soft tissues. Figure 2b – The sagittal image shows the extent of the erosion of the vertebral body and enlargement of the intervertebral foramen (case 2).

elliptical nuclei. Numerous mast cells located close to and at a distance from the vascular capillaries were identified by the presence of metachromasia.

Ultrastructural analysis. Electron microscopy revealed fewer cells than in a neurinoma. At least three different types were identified: cells resembling Schwann cells, perineurial or fibroblast-like cells, and mast cells.

The Schwann cells had very large nuclei surrounded by dense chromatin, a clear scanty cytoplasm and a pronounced basal lamina (Fig. 6a).

The fibroblast-like cells were fusiform with an elongated nucleus and had fine, folded cytoplasmic processes at either end which were frequently electro-dense (Fig. 6b), unlike the Schwann cells which always had clear cytoplasm. The perinuclear area of the cytoplasm contained few mitochondria, a scanty folded endoplasmic network and an extensive Golgi apparatus. Microfilaments and microtubules were, however, conspicuously present in the cell processes together with numerous pinocytotic vesicles. The basal lamina was

Fig. 3a

Fig. 3b

MR coronal (a) and sagittal (b) T1-weighted images after injecting gadolinium DTPA show an intradural soft-tissue mass at D12. The mass has intensity signals slightly higher than those of muscle and multiple areas of decreased signal intensity centrally. The CSF below the neurofibroma is more intense than that above due to the increase in the protein concentration in the trapped fluid (case 1).

Fig. 4a

Fig. 4b

The surgical removal of a spinal neurofibroma. Figure 4a - Laminectomy and wide opening of the dura is necessary to expose the neoplasm completely. Figure 4b - The dura is meticulously sutured after removal of the mass (case 2).

Fig. 5a

Fig. 5b

Figure 5a - Histological examination shows hyperplasia of the interfascicular connective tissue. The matrix is rich in proteoglycans and there are numerous tightly packed collagen and reticular fibres. The predominant cells are elongated with elliptical nuclei ($\times 50$). Figure 5b - There are numerous areas of myxoid degeneration in the proliferating connective tissue and hyperplasia of the vascular stroma ($\times 10$).

Fig. 6a

Fig. 6b

Fig. 6c

Fig. 6d

Figure 6a - Electron micrograph showing Schwann cells with very large nuclei, dense chromatin surrounding the nuclear membrane, clear scanty cytoplasm and a pronounced basal lamina ($\times 10\,000$). Figure 6b - Fusiform fibroblast-like cells have elongated nuclei and fine, folded cytoplasmic processes at either end. These cytoplasmic processes are often electron dense. The perinuclear area of the cytoplasm contains very few mitochondria, a scanty folded endoplasmic network and an extensive Golgi apparatus. Microfilaments and microtubules are conspicuous in the cell processes together with numerous pinocytotic vesicles. The basal lamina is fragmented or even absent and the extracellular compartment contains numerous collagen fibrils interspersed with areas of myxoid tissue ($\times 6000$). Figures 6c and 6d - Numerous mast cells arranged near the perineurial cells and at a distance from the Schwann cells. The mast cells can be recognised by their central nuclei, peripherally dense chromatin and numerous intracytoplasmatic electron dense granules. The plasma membrane has short processes which are closely interlocked with the fine elongated processes of the perineurial cells ($\times 4500, 5750$).

discontinuous, fragmented or even absent and the extracellular compartment contained numerous collagen fibrils variously arranged and interspersed with areas of myxoid tissue.

Mast cells (Figs 6c,d) were relatively numerous and characteristically were arranged near the perineurial cells and at a distance from the Schwann cells. They had a central nucleus with dense peripheral chromatin and numerous intracytoplasmic electron-dense granules. The plasma membrane contained short processes which were closely interlocked with the fine elongated processes of the perineurial cells.

DISCUSSION

Since solitary neurofibroma at any site has been only recently defined as a clinical entity and is still controversial, it is not surprising that there is even more uncertainty and confusion as regards its rare appearance in the spine. As we have already emphasised, the problems are not only due to the confused terminology but also to the absence of a precise clinical and pathological classification.

Some authors (Okazaki and Scheithauer 1988; Sbrocca et al 1989) have claimed that about 90% of central and peripheral neurofibromas are solitary and are unrelated to systemic neurofibromatosis. Others have suggested that the neurofibroma is the typical and exclusive lesion of von Recklinghausen's disease and even when apparently solitary should be regarded as evidence of that disease (Russell and Rubinstein 1989).

We feel that the many cases reported in the literature of solitary neurofibroma in the absence of neurofibromatosis cannot be ignored (Chomette et al 1984; Noterman, Ballaux and Dor 1984; Okazaki and Scheithauer 1988; Sbrocca et al 1989; Viard et al 1989; Hillstrom, Zarbo and Jacobs 1990) and our observations confirm that although rare, the solitary form of spinal neurofibroma does occur. Moreover, we have identified some radiographic, histological and ultrastructural characteristics which allow differentiation from other neoplastic lesions and from neurinoma in particular.

MRI with its high definition of soft tissues and its ability to obtain multiple plane images allows preoperative differentiation of several types of spinal tumour, particularly of neurinoma, neurofibroma, meningioma and haemangioma (Takemoto et al 1988). In our three cases the T1-weighted image gave a slightly higher signal than muscle and an increased T2-weighted signal but with many central areas where the signal was decreased. After injection of gadolinium DTPA contrast the tumours showed a bright peripheral enhancement and non-uniform contrast in the central areas. Similar observations were reported by Burk et al (1987) in seven patients with spinal neurofibroma in neurofibromatosis and they suggested that these MRI findings were specific to neurofibroma.

The histological findings in our cases explain the CT and MR images. The proteoglycan-rich matrix, the areas of myxoid degeneration and fibroconnective tissue proliferation and the hyperplasia of the vascular stromal component match the tomographic analysis, and the high water content of the neoplastic matrix explains the increased signal in the T2-weighted images. The lack of homogeneity of the signal in the central area can be attributed to the high density of the poorly cellular fibrous tissue within the tumour.

With regard to treatment, some authors have preferred a conservative surgical approach with only partial removal of the tumour if it is intramedullary or involves important nerve roots (Gautier-Smith 1967; Salah, Horcajada and Perneczky 1975; Stein 1985). We agree, however, with Kim et al (1989) that with a wide surgical exposure, radical excision can be achieved without nerve damage. 'False recurrence' has often been described after incomplete removal of the neoplasm (Schiffer and Fabiani 1970) and it is necessary to beware of intradural extension in lesions which are apparently exclusively extradural, because of the frequency of hour-glass tumours.

Histological and ultrastructural analysis has demonstrated in the spine those same differences between neurofibroma and neurinoma which we have previously reported in peripheral nerves (Sanguinetti et al 1991). The predominant cell type of the neurofibroma is a perineurial cell with long bipolar or tripolar electron-dense cytoplasmic processes, fragmentation of the basal lamina and containing numerous pinocytotic vesicles. If the presence of a more conspicuous amount of loose connective tissue is excluded, there were no histological differences between peripheral and spinal neurofibromas.

Besides the theoretical interest of identifying the solitary spinal neurofibroma as a separate neoplasm, there is also the clinical and prognostic importance. Whereas malignancy can be excluded for a neurinoma (Carstens and Schrodt 1969; Guccion and Enzinger 1979) and is extremely rare for a solitary neurofibroma (Okazaki and Scheithauer 1988) it is nevertheless quite common in multiple neurofibromas (Stout 1958; Poirier et al 1968; Russell and Rubinstein 1989).

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