Eur Spine J (2003) 12 : 328–331
DOI 10.1007/s00586-002-0484-9

CASE REPORT

D. F. O'Brien
M. Farrell
J. P. Fraher
C. Bolger

Schwann cell invasion of the conus medullaris: case report

Received: 24 April 2002
Revised: 26 June 2002
Accepted: 3 July 2002
Published online: 19 November 2002

Declaration: The Wellcome Trust has assisted Professor Fraher on a series of other studies concerning the transitional zone over many years. No direct financial assistance of any kind has been received for this case report, nor is there any vested interest in its publication.

D.F. O'Brien (✉) · C. Bolger
Department of Neurosurgery,
Beaumont Hospital, Dublin 9, Ireland
e-mail: neurosurgery.tleader@beaumont.ie,
Tel.: +353-1-8377755,
Fax: +353-1-8092302

M. Farrell
Department of Neuropathology,
Beaumont Hospital, Dublin, Ireland

J.P. Fraher
Department of Anatomy
and Biosciences Research Institute,
National University of Ireland, Cork, Ireland

Abstract As Schwann cells possess regenerative capabilities there is intense interest concerning their role in central nervous system (CNS) regeneration. We report on a case of an intramedullary schwannoma involving the conus medullaris and spinal cord above it. We discuss the possible origin of these cells and the mechanisms by which these cells may invade the CNS. We offer imaging and discuss experimental studies to support our hypothesis. This case concerns a 48-year-old man, who presented with a 6-month history of bilateral lower extremity weakness. Magnetic resonance imaging (MRI) revealed an intramedullary tumour extending from the conus to T11. At operation, following laminectomy and durotomy, a schwannoma was dissected free from the conus. Total gross resection of tumour was achieved. The patient made an uneventful and full recovery. This case shows that Schwann cells can invade the CNS. Manipulation of the transitional zone astrocytic barrier may offer a potential avenue for Schwann cells to enter the CNS in pathological states.

Keywords CNS regeneration · Intramedullary schwannoma · Transitional zone

Introduction

As it is traced centrally towards the spinal cord surface, each dorsal spinal nerve root divides into a number of rootlets (Fig. 1a,b). Each of these is attached separately to the spinal cord surface. The area to which all the constituent rootlets of a given root are attached is its attachment zone. In the mature rat the dorsal rootlets are closely packed; they are apposed to one another, being separated by partitions composed of rootlet sheath cells [13]. In man, a similar arrangement holds [22].

An irregularly tapering, approximately conical, central tissue projection (CTP) extends distally into the proximal part of each rootlet (Fig. 1c) [12]. Thus, central and peripheral nervous tissues interdigitate and overlap along a segment of rootlet. A length of rootlet therefore contains both central nervous system (CNS) and peripheral nervous system (PNS) tissues. This is termed the CNS-PNS transitional zone (TZ), which lies within the rootlet itself (Fig. 1c). The surface of the CTP comprises the CNS-PNS interface (Fig. 1d). This is formed of astrocyte processes and comprises an elaboration of the glia limitans, which defines the outer limit of the spinal cord and is covered by a basal lamina. The primary afferent axons traverse perforations in this as they pass from the PNS tissue compartment into the CNS (Fig. 1d). At the interface there is a sharp discontinuity in a variety of tissue types. Peripheral

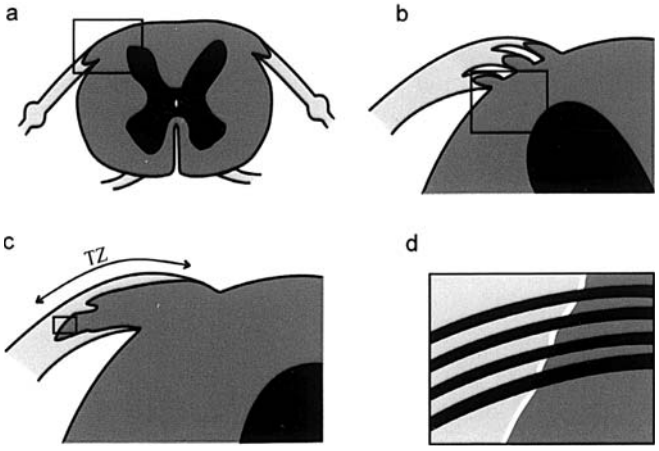

Fig. 1 Diagrams with successive enlargements of the areas outlined, showing **a** transversely sectioned spinal cord, **b** dorsal root attachment to the spinal cord by means of rootlets, **c** interdigitation of central nervous system (CNS) and peripheral nervous system (PNS) tissues along the length of rootlet, termed the transitional zone (TZ), and **d** the CNS-PNS interface, showing individual axons passing between the two tissue compartments. This is reproduced in part from Gilmore et al. [17], with permission from the editors H A Aldskogius and J P Fraher (*pale* PNS tissue, *intermediate* CNS white matter, *dark* CNS grey matter)

to it, axons are myelinated by Schwann cells and the supporting tissue is endoneurium. Central to it, oligodendrocytes form the myelin sheaths, and fibres are separated to a variable degree by astrocytic tissue.

It has long been recognised that dorsal and ventral root TZ Schwann cells may, in certain situations, migrate into the spinal cord, especially in response to cord injury [16, 17, 28]. The role of Schwann cells in the CNS is unclear, but it has been suggested that their presence may impede regeneration following spinal cord injury [8]. Conversely, other studies have used PNS grafts to support axonal elongation across transection lesions in adult rat spinal cord [6, 21]. It has been shown that Schwann cell populations, when grafted into the injured spinal cord, subsequently ensheath the regenerating axons entering the graft [26]. Furthermore, Schwann cells possess a basal lamina, which contains extracellular matrix molecules that promote nerve fibre growth [1].

In tissue sections the invading Schwann cells are easily recognised as tumourlets. Rarely, these clusters of invading Schwann cells may enlarge and become indistinguishable from a schwannoma. Similar Schwann cell invasion may be present in patients with neurofibromatosis [23]. On the other hand, glial cells have been detected in the PNS, particularly in the ventral roots, as islands of cells [11].

The following case report serves to further highlight the fact that the TZ is not an impenetrable barrier, but one that can in certain conditions be breached by Schwann cells. Manipulation of this barrier to aid Schwann cell invasion of the injured or demyelinated cord offers a possible future therapeutic strategy. This report underlines the close relationship between basic and clinical neuroscience as well as the potential for these together to address the central clinical problems.

Case report

A 48-year-old man presented with a 6-month history of bilateral lower extremity weakness affecting the right side more than the left. Numbness was present along inner and outer aspects of the

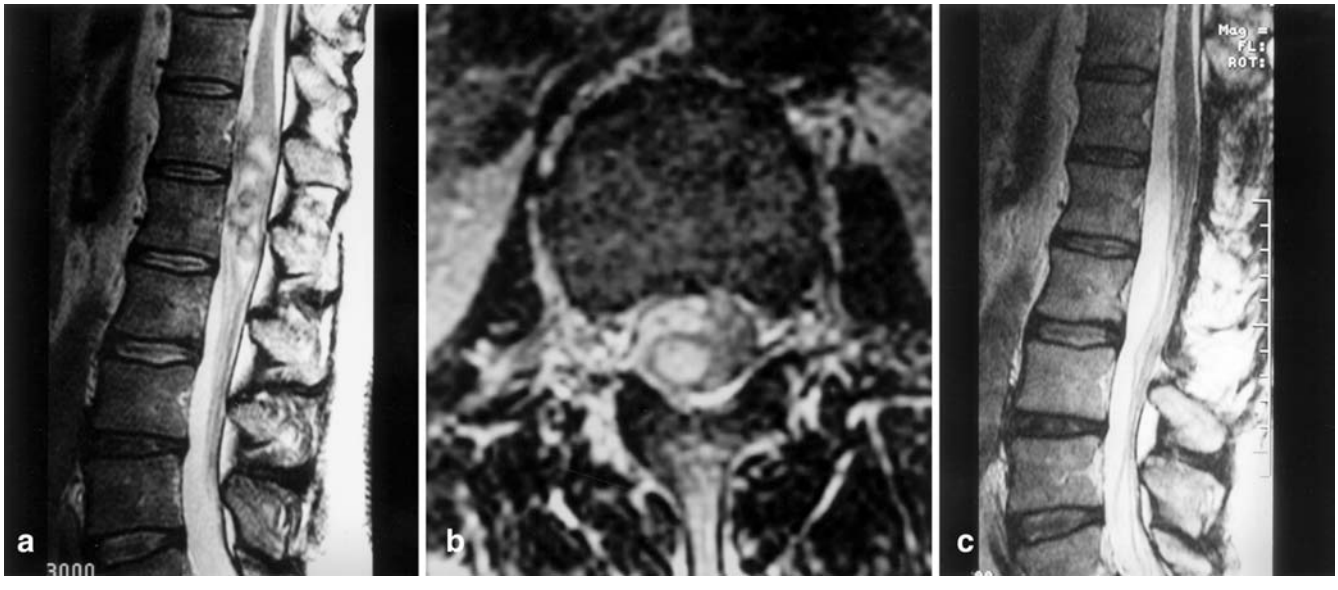

Fig. 2 **a** Sagittal T2-weighted magnetic resonance (MR) image of thoraco-lumbar spine showing a high-signal lesion extending from the lower border of the cord at L1 to the mid-T12 level. **b** Axial scan through the upper extent of the tumour shows its central and right-sided intramedullary location. **c** A post-operative sagittal MR image shows no evidence of any residual tumour

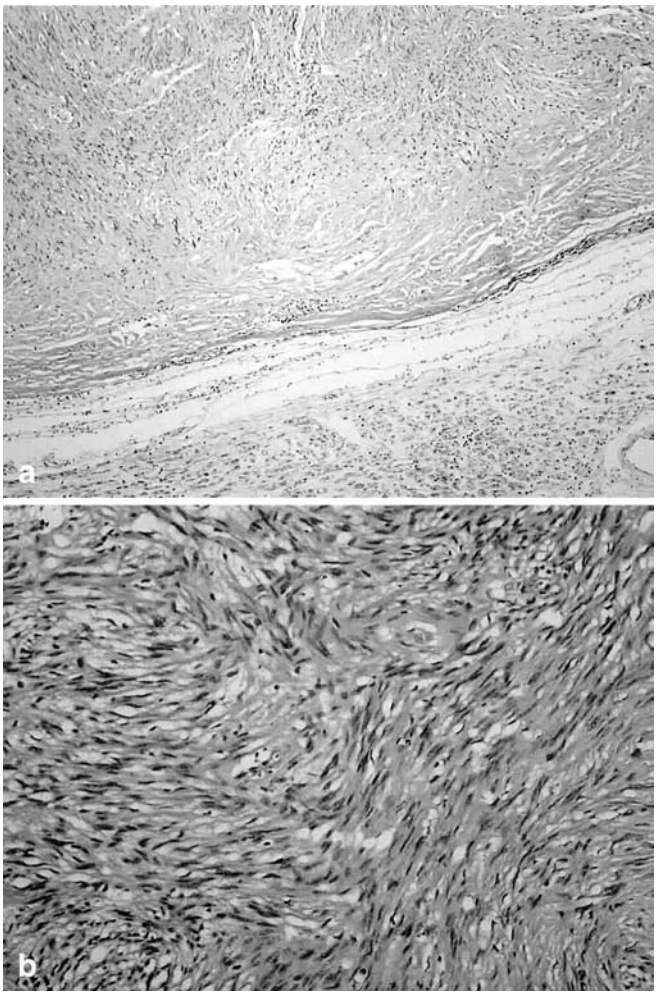

Fig. 3 **a** Low-power view of the tumour with nerve root in lower aspect of section adherent to the tumour surface. **b** A high-power view of schwannoma, which demonstrates interlacing bundles of spindle cells having long tapering cytoplasmic processes

right leg. Deep tendon reflexes of the right knee and right ankle were reduced. The right plantar response was extensor. There were no features of neurofibromatosis.

Magnetic resonance imaging (MRI) of the entire neuraxis revealed an intramedullary tumour extending from the conus medullaris at the lower border of L1 to the upper border of T11 (Fig. 2a,b).

At operation, image intensification was used to localize the T11, T12 and L1 vertebral levels. A three-level laminectomy was performed to expose the T11, T12 and L1 regions. A midline durotomy revealed a diffusely swollen spinal cord. Under the operating microscope, a tumour was clearly seen arising from the right-sided nerve roots of the cauda equina at the lower border of L1. The tumour invaded the conus medullaris as well as the right side and centre of the cord above it. An intra-operative frozen section report suggested a schwannoma. A dorsal midline myelotomy was used to expose the tumour, which was fully excised using sharp microscopic dissection and a micro-ultrasonic aspirator. A full macroscopic excision of the tumour was achieved. The patient made an uneventful recovery from surgery and was without neurological deficit. A 6-months post-operative MR image of the spine shows no evidence of recurrent tumour (Fig. 2c).

Histological examination of the resected tumour revealed a densely cellular non-glial derived neoplasm in which cells were large with plump spindle-shaped nuclei and long tapering cytoplasmic processes (Fig. 3a,b). Cells were arranged into ill-defined interwoven fascicles. Rare verocay-like bodies were present. There was no evidence of tumour necrosis and mitotic figures were not present. Immunohistochemistry was negative for glial fibrillary acidic protein, but S-100 was positive. The features were those of a schwannoma.

Discussion

Spinal intramedullary schwannomas have been described both in association with and independent of neurofibromatosis [4, 5, 7, 10, 23, 24]. They have been estimated to represent 0.3% of all intraspinal tumours. A recent review of the MRI findings of 14 intramedullary spinal schwannomas showed that the lower thoracic spinal cord is amongst the least common sites for their occurrence [27]. Subtotal excision leads to recurrence, and the importance of accurate intra-operative frozen section reports is emphasized in order to attempt a full tumour clearance [7].

Clusters of cells are found on developing ventral rootlets [13, 14]. These may act as a pluripotential source of cells. Some of these differentiate into Schwann cells, which ensheath and myelinate axons of the ventral rootlets. There is evidence that others leave the clusters but fail to ensheath axons. These ectopic Schwann cells have each their own covering of basal lamina. They come to lie in the rootlet endoneurium or in the adjacent pia mater, close to the CNS-PNS interface (Fraher and Kaar, unpublished). There are corresponding clusters at the dorsal rootlet transitional zone (DRTZ) [9, 13, 18, 19, 20]. These form boundary caps. There is evidence to suggest that these may influence the entry of dorsal root axons into the early spinal cord. Their eventual fate in dorsal rootlets is unclear. However, it may be that the clusters disaggregate here too, and give rise to Schwann cells [15]. It is therefore possible that, as at ventral rootlets, some of them fail to enfold dorsal rootlet axons. Neoplastic proliferation of such cells is a possible source of tumours at TZs, including that of cranial nerve VIII, where they could give rise to acoustic neuromas, as well as at the DRTZ. They could therefore arise from Schwann cells with an ectopic pial location. Such a location for them is suggested by the finding that the pia mater also stains with nerve growth factor receptor, an embryonic Schwann cell marker [29].

Invasion of the cord by such neoplasms would entail their growth centrally through the dorsal rootlets as far as the CNS-PNS interface. On reaching this, the tumour cells could displace the CNS tissue and invaginate it centrally, through the rootlet and then into the cord itself. Alternatively, the Schwann cells could intermingle with CNS tissue. This would involve their penetration of the CNS-PNS interface. A series of immunohistochemical observations has shown an intense staining of the glia limitans, with nerve cell adhesion factor (NCAM), [25]. It is possible that

Schwann cell tumour cells could achieve penetration by secreting factors that denature NCAM at the glia limitans and allow tumour penetration of the TZ.

The tumour could also have arisen from ectopic Schwann cells within the CNS. These are not uncommon and their numbers increase with age. They could have been derived from Schwann cells of perivascular nerve bundles. The paucity of blood vessels in the DRTZ region perhaps argues against this [2, 3]. However, they could also arise as a result of interruption of the glia limitans associated with minor traumata of the TZ, perhaps associated with mild repeated traction injuries of the roots.

Irradiation of the spinal cord creates a glial deficient spinal cord. This is associated with Schwann cell invasion of the cord as the glia limitans loses its constituent cells [16, 28]. It has been shown that dorsal root axons can regrow into such an environment [28]. It is interesting to speculate on the potential for radiosurgery to precisely create such an environment in humans. Further work on the immunohistochemistry of the TZ and its response to antibody application is indicated.

Conclusion

The perception that Schwann cells are never present in the CNS is false. This case report illustrates an intramedullary schwannoma of the thoracic spinal cord. Manipulation of the transitional zone astrocytic barrier at both cranial and spinal levels may in future provide a therapeutic strategy to aid remyelination in various pathological conditions of the CNS.

References

1. Ard MD, Bunge RP, Bunge MB (1987) Comparison of the Schwann cell surface and the Schwann cell extracellular matrix as promoters of neurite growth. J Neurocytol 16:539–555
2. Berthold C-H, Carlstedt T (1997) Observations on the morphology at the transition between the peripheral and the central nervous system in the cat. II. General organisation of the transitional region in S_1 dorsal rootlets. Acta Physiol Scand 446:23–42
3. Berthold C-H, Carlstedt T (1997) Observations on the morphology at the transition between the peripheral and the central nervous system in the cat. III. Myelinated fibres in S_1 dorsal rootlets. Acta Physiol Scand 446:43–60
4. Beskonaki E, Cayli S, Turgut M, Bostanci U, Seckin S, Yalcinlar Y (1997) Intraparenchymal schwannomas of the central nervous system: an additional case report and review. Neurosurg Rev 20:139–144
5. Binatli O, Ersahin Y, Korkmaz O Bayol U (1999) Intramedullary tumour of the spinal cord. A case report and review of the literature. J Neurosurg Sci 43:163–167
6. Bjorklund A (1994) Long distance axonal growth in the adult central nervous system. J Neurosurg 242:S33–S35
7. Botelho CH, Kalil RK, Masini M (1996) Spinal cord schwannoma: case report. Arq Neuropsiquiatr 54:498–504
8. Bruce JH, Norenberg MD, Kraydieh S, Puckett W, Marcillo A, Dietrich D (2000) Schwannosis: role of gliosis and proteoglycan in human spinal cord injury. J Neurotrauma 17:781–788
9. Carlstedt T (1981) An electron-microscopical study of the developing transitional region in feline S1 dorsal rootlets. J Neurol Sci 50:357–372
10. Duong H, Tampieri D, Melancon D, Salazar A, Robert F, Alwatban J (1995) Intramedullary schwannoma. Can Assoc Radiol J 46:179–182
11. Fraher JP (1974) Longitudinal study of probable glial islands. J Neuropathol Exp Neurol 33:552–560
12. Fraher JP (1992) The CNS-PNS transitional zone in the rat. Morphometric studies at cranial and spinal levels. Prog Neurobiol 38:261–316
13. Fraher JP, Rossiter JP (1983) Cell clusters on developing rat ventral roots. Prenatal development. J Anat 136:111–128
14. Fraher JP, Rossiter JP (1983) Cell clusters on rat ventral roots. II. Postnatal development. J Anat 137:55–571
15. Fraher JP, Sheehan MM (1987) The CNS-PNS transitional zone of rat cervical roots during development and at maturity. A morphological and morphometric study. J Anat 150:145–154
16. Gilmore SA, Sims TJ (1997) Glial-glial and glial-neuronal interfaces in radiation-induced, glia depleted spinal cord. J Anat 190:5–21
17. Gilmore SA, Sims TJ, Houlé JD Glial boundaries in experimentally manipulated spinal cords. In: Aldskogius HA, Fraher JP (eds) Glial barriers and CNS regeneration. IOS Press (in press)
18. Golding JP, Cohen J (1997) Border controls at the mammalian spinal cord: late-surviving neural crest boundary cap cells at dorsal root entry sites may regulate sensory afferent ingrowth and entry zone morphogenesis. Mol Cell Neurosci 9:381–396
19. Golding, JP, Shewan D, Berry M, Cohen J (1996) An in vitro model of the rat dorsal root entry zone reveals developmental changes in the extent of sensory axon growth into the spinal cord. Mol Cell Neurosci 7:191–203
20. Golding JP, Shewan D, Cohen J (1997) Maturation of the mammalian dorsal root entry zone – from entry to no entry. Trends Neurosci 20:303–308
21. Guth L (1975) History of central nervous system regeneration research. Exp Neurol 99:154–165
22. Hynes PJ, Fraher JP, O'Sullivan VR (1993) Segment length and root orientation in normal and sacrally attached spinal cords. A morphometric study. Clin Anat 6:167–172
23. Lee M, Rezai AR, Freed D, Epstein F (1996) Intramedullary spinal cord tumours in neurofibromatosis. Neurosurgery 38:32–37
24. Lee DY, Chung CK, Kim HJ (1999) Thoracic intramedullary schwannoma. J Spinal Disord 12:174–176
25. O'Brien DF, Dockery P, McDermott K, Fraher JP (2001) Early development of rat ventral root transitional zone: an immunohistochemical and morphometric study. J Neurocytol 30:11–20
26. Paino CL, Bunge MB (1991) Induction of axon growth into Schwann cell implants grafted into lesioned adult rat spinal cord. Exp Neurol 114:254–257
27. Riffaud L, Morandi X, Massengo S, Carsin-Nicol B, Heresbach N, Guegan Y (2000) MRI of intramedullary spinal schwannomas: case report and review of the literature. 42:275–279
28. Sims TJ, Gilmore SA (1994) Regrowth of dorsal root axons into a radiation-induced glial-deficient environment in the spinal cord. Brain Res 634:113–126
29. Yan, Q, Johnson EM (1988) An immunohistochemical study of the nerve growth factor receptor in developing rats. J Neurosci 8:3481–3498