

## Relation of Multiple Neurogenic Tumors in the Spinal Canal to Neurofibromatosis

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**Objective :** The authors characterize a syndrome of multiple neurogenic tumors in the spinal canal, which is unclassifiable by the current National Institute of Health(NIH) criteria for neurofibromatosis.

**Methods :** We retrospectively examined cases in which two or more spinal neurogenic tumors were detected by magnetic resonance(MR) imaging and which had been pathologically confirmed. Eighteen patients were recruited between February 1986 and March 2002. According to NIH criteria, eight cases were neurofibromatosis type 1(NF1), four were type 2(NF2), and six were neither type 1 nor type 2 (Unclassifiable : UC). The locations of lesions, clinical presentations, radiological findings, and pathological results with immunohistochemistry were reviewed.

**Results :** In the case of NF2, three of four cases were intradural tumors. Pathological examinations revealed neurilemmomas in two of four NF2 and all of the UC cases. In the case of NF1, pathological examinations showed seven neurofibromas and one neurilemmoma. Concerning UC, the age at presentation was middle-aged to late (mean age 48.5, range 35 to 64), which contrasted with ordinary NF2, where patients tended to become symptomatic before 20years of age. The pathological examinations of UC cases revealed neurilemmoma similar to most of NF2 and the immunohistochemical study showed characteristic of NF1.

**Conclusion :** Multiple neurogenic tumors in the spinal canal are an under-recognized disease entity. Further studies for genetic aberration in multiple spinal neurogenic tumors are needed.

**KEY WORDS :** Multiple · Neurogenic tumor · Neurofibromatosis · Spinal canal.

### Introduction

In neurosurgical practice, multiple neurogenic tumors are encountered occasionally in approximately 3 to 4% of patients with spinal or peripheral tumors<sup>7,9,20</sup>. However, no study has yet presented a definite diagnostic difference between neurofibromatosis and unclassifiable multiple neurogenic tumors in the spinal canal. To characterize the syndrome of multiple neurogenic tumors in the spinal canal, which is presently unclassifiable by the current National Institute of Health (NIH) criteria for neurofibromatosis<sup>12</sup>, the authors performed a retrospective analysis in patients with two or more spinal neurogenic tumors.

### Materials and Methods

#### Patient population

Between February 1986 and March 2002, eighteen patients having two or more neurogenic tumors in the spinal canal were recruited for this study.

There were ten males and eight females; patients' ages ranged from 2 to 64years (mean age, 35years). The cases included in our series were selected using the following criteria. 1) Two or more suspected neurogenic tumors by magnetic resonance imaging in the spinal canal. 2) Cases having only one lesion in the spinal canal with neurofibromatosis or cases not proven by surgery were excluded.

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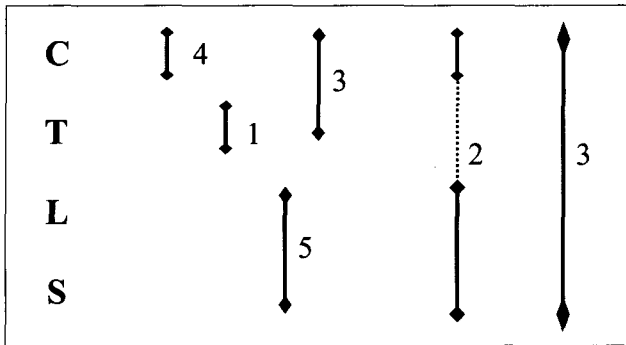
**Table 1.** Clinical summary of eighteen patients with multiple spinal neurogenic tumors

Case No	Age(yrs) at surgery, Sex	Neurofibromatosis type by NIH criteria	Presenting symptoms & signs	Tumors found at first			Tumors found at follow up			Follow up (months)	Pathological diagnosis
				Intra-cranial	Spinal/operated	Peri-pherical	Intra-cranial	*Spinal operative result	Peri-pherical		
1	57/F	?	gait disturbance, lt. hemiparesis	r/o multiple meningioma	C4-T1, L1-2, T10-12, L5 IDEM	lt. popliteal fossa mass	r/o multiple meningioma : no change	GTR, GTR	GTR	2	all neurilemmoma
2	14/M	2	gait disturbance, hoarseness	bilateral CPA mass	C1-2, ED, ES, LS ID/C1-2	0	GKS	STR	0	11	meningioma
3	41/M	?	quadriparesis, lt. hearing loss	lt. CPA mass	C5-7 IDEM & foraminal/ C5-7	0	STR	STR	lt. hand soft tissue mass : GTR	176	all neurilemmoma
4	45/M	2	neck pain	bilateral CPA mass	C7-T1 IDEM, T1-2 foraminal/C7-T1	0	no change	GTR	0	17	neurilemmoma
5	46/F	1	paraplegia	?	C2-3 IDEM, T11-12 IDEM, LS ID/T11-12, LS	retroperitoneal mass	?	GTR, GTR	PR	3	all neurilemmoma
6	14/F	2	incidental mass	bilateral CPA mass	C6-T2 IDEM/C6-T2	intrathoracic mass	no change	GTR	Bx	55	C6-T2 : plexiform neurofibroma/thoracic : neurilemmoma neurofibroma
7	28/M	1	lt. hemiparesis	?	C1-2 IDEM, C3-4 ES/C1-2	0	?	STR	0	13	all neurofibroma
8	2/F	1	floppy infant	?	LS ED & ES/LS	presacral	?	STR	STR	46	all neurofibroma
9	24/M	1	back pain & both leg radiating pain	rt. thalamic dysplastic lesion	LS ED & ES/LS	0	?	Bx	0	4	myxoid neurofibroma
10	24/F	1	back pain & lt. leg radiating pain	?	L multiple ID/L4	0	?	GTR	0	1	neurofibroma
11	24/M	1	gait disturbance	?	C1-3 IDEM, C4-5, C5-6 ID/C1-3	neck, mediastinum, chest	?	GTR	?	6	plexiform neurofibroma
12	36/M	?	back pain & both leg radiating pain	?	C1-2, T1-3 IDEM/T1-3	0	?	GTR	0	13	neurilemmoma
13	35F	?	both hand paresthesia	0	C1-2 ED, T2-4 ED, L3 foraminal, S1 ID/C1-2, T2-4, S1	lt. arm, shoulder, neck mass	?	GTR, GTR, GTR	GTR, GTR, GTR	16	all neurilemmoma
14	27/M	1	lt. hemiparesis	?	C5-6 IDEM, C7-8 foraminal/C5-6	chest nodule	?	STR	Bx	18	all neurofibroma
15	37/M	1	paraparesis	?	T ED, ES/T : 5 surgery	0	?	GTR, 4 STR	0	143	neurofibroma/ 4 malignant neurofibroma
16	58/F	?	back pain & both leg, radiating pain, rt HL	rt. CPA mass	L1-2 IDEM/L1-2	0	GTR	GTR, New C1-2 IDEM : GTR	0	27	all neurilemmoma
17	64/F	?	neurogenic bladder	?	L1-2 IDEM, L4-5 ID/L1-2	0	?	GTR	0	2	neurilemmoma
18	56/M	2	paraparesis	bilateral CPA mass	C6-7 IDEM, L3 ID, L5-S1 ID/C6-7	bilateral forearm mass, lt. parotid gland mass	?	GTR	GTR, GTR	117	all neurilemmoma

\* Concerning the spinal level for which decompressive operation were performed. M : Male, F : Female, NIH : National Institutes of Health, rt : right, lt : left, HL : Hearing Loss, CPA: CerebelloPontine Angle, C : Cervical, T : Thoracic, L : Lumbar, S : Sacral, LS : LumboSacral, IDEM : IntraDural ExtraMedullary, ED : ExtraDural, ES : ExtraSpinal, ID : IntraDural, GKS : GammaKnife Surgery, STR : SubTotal Removal, GTR : GrossTotal Removal, Bx : Biopsy, PR : Partial Removal, KPS : Karnofsky Performance Scale

**Neurodiagnostic studies**

Radiological evaluation consisted of magnetic resonance (MR) imaging of the spine and /or brain MR imaging. Spinal MR images were obtained and reviewed in all cases, while



**Fig. 1.** The number of cases according to level of tumors by preoperative magnetic resonance images.

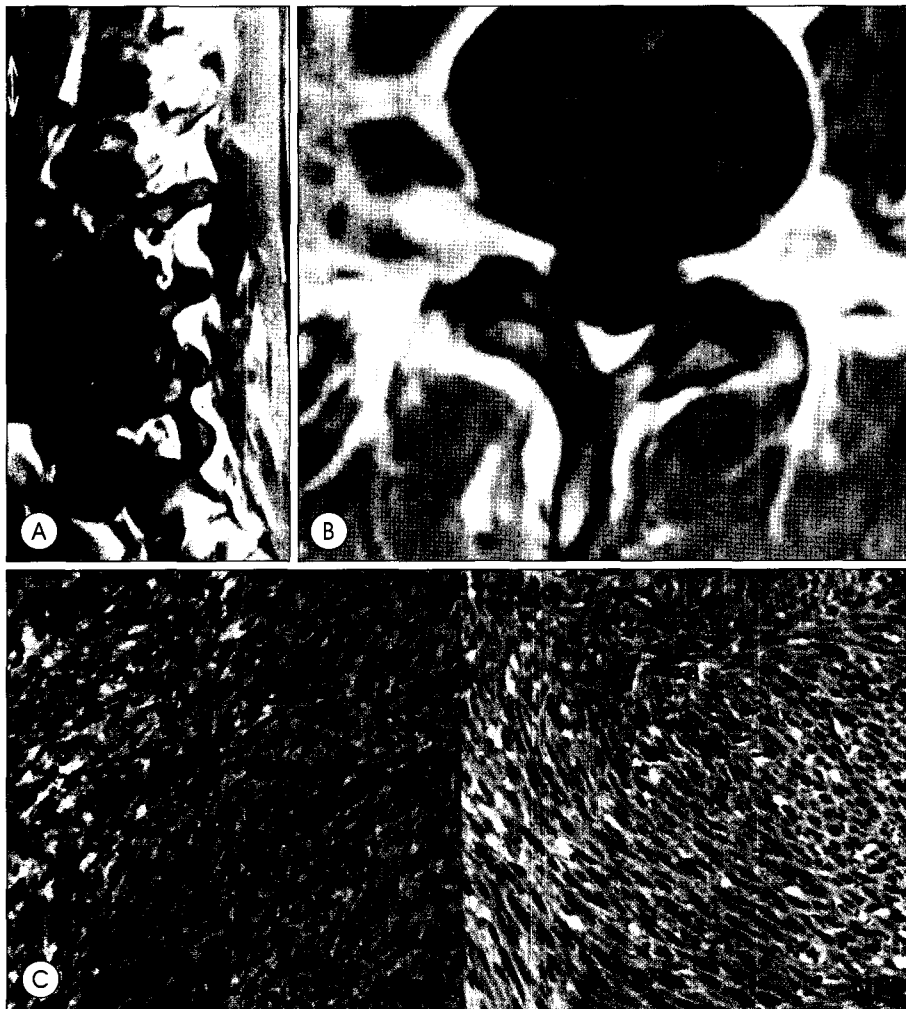
brain MR images were obtained and reviewed in four cases. Of the multiple tumors, intradural tumors were seen in thirteen cases (cases 1, 3, 4, 5, 6, 7, 10, 11, 12, 14, 16, 17, and 18), extradural tumors in four (cases 2, 8, 9, and 15), and intradural and extradural tumors in one (case 13). The lesion locations are summarized in Table 1.

**Histopathology and immunohistochemistry**

All histopathology was reviewed by two pathologists of the authors, one of whom was blinded to both the original pathological diagnosis and the clinical features of the cases.

After reviewing the materials, immunohistochemical study was performed. For this, tissue array block was made from a representative formalin (cold 10% buffered) fixed and paraffin-embedded tissue, which were cut into 2~3µm thickness. Anti-NF1 (neurofibromin) antibody (mouse monoclonal antibody, Zymed, South San Francisco, U.S., 35-6900; dilution 1:200) and anti-NF2 (schwannomin) antibody (rabbit polyclonal antibody, Santa Cruz, California, U.S. sc-331; dilution 1:200) were used as primary antibodies.

After reviewing the materials, immunohistochemical study was performed. For this, tissue array block was made from a representative formalin (cold 10% buffered) fixed and paraffin-embedded tissue, which were cut into 2~3µm thickness. After deparaffinization and rehydration, the sections were subjected to high temperature antigen unmasking in a citrate buffer in the autoclave (121°C) for 20min. After blocking in 2% skimmed milk, the sections were incubated with primary antibodies with ideal dilution for 60min. at room temperature. The sections were incubated with biotinylate secondary antibody, which is polyvalent and universal (prediluted, DAKO), and the expression was detected using the peroxidase labeled streptavidin biotin complex technique according to the manufacturer's recommendations. Hematoxylin counter staining was performed. Known schwannoma and peripheral nerve served as the positive tissue control for both antibodies. For antibody control, primary antibodies were omitted. Strong nuclear and cytoplasmic staining was regarded as positive staining. We classified the stainability as three tiered grading



**Fig. 2.** Case 9 (NF1 case). A : Preoperative sagittal gadolinium-enhanced T1-weighted magnetic resonance image, demonstrating multiple enhancing lesions at lumbar level, mainly the largest tumor arising from L3-4 level. B : Axial enhanced image at L3-4, showing right extradural, foraminal, and extradural tumor. C : Immunohistochemically, this NF1 case does not express neurofibromin, i.e., loss of NF1 (Left) (X200), but expresses schwannomin (NF2, Right)(X200).

(1+ to 3+) according to the intensity and distribution of positive staining.

## Results

The clinical features of our patients are summarized in Table 1. Mean follow-up in our series was 35 months (range, 1 to 176 months). Eight cases (cases 5, 7, 8, 9, 10, 11, 14, and 15) satisfied the criteria of the National Institute of Health (NIH) for neurofibromatosis type 1 (NF1), four cases (cases 2, 4, 6, and 18) satisfied type 2 (NF2), and the remaining six (cases 1, 3, 12, 13, 16, and 17) were unclassifiable (UC). All patients presented with pain and/or neurological deficits.

The patients were examined clinically to detect neurological abnormalities, skin manifestations, or peripheral tumors and questioned about a family history of central nervous system tumors. Hospital records were reviewed for presenting symptoms, signs, and functional status preoperatively and at the last follow-up. Presenting symptoms were as follows (Table 2): pain, sensory changes such as paresthesia or hypesthesia, gait disturbance, paraparesis, quadriparesis, hemiparesis, and voiding difficulty. Mean symptom duration was 8.1 months (range, 1 to 60 months). Locations and vertebral involvement were ascertained from radiological and operation records.

Two cases (case 11, 14) of NF1 showed a familial history of neurofibromatosis, though no familial history of spinal tumor was observed in the other cases.

The location of tumors was summarized in Figure 1. Four cases (cases 3, 7, 11, and 14) showed multiple cervical tumors only. Thoracic level multiple tumors were seen in one case (case 15), and lumbosacral tumors in five cases (cases 8, 9, 10, 16, and 17). Cervical and thoracic tumors were found in three cases (cases 4, 6, and 12), cervical and lumbosacral tumors in two cases (case 2, and 18), and whole spinal multiple tumors in two cases (cases 1, 5, and 13).

Radiological images of illustrative cases were presented in Figure 2, Figure 3, and Figure 4. In case 9 (NF1), MR images showed multiple enhancing lesions, mainly

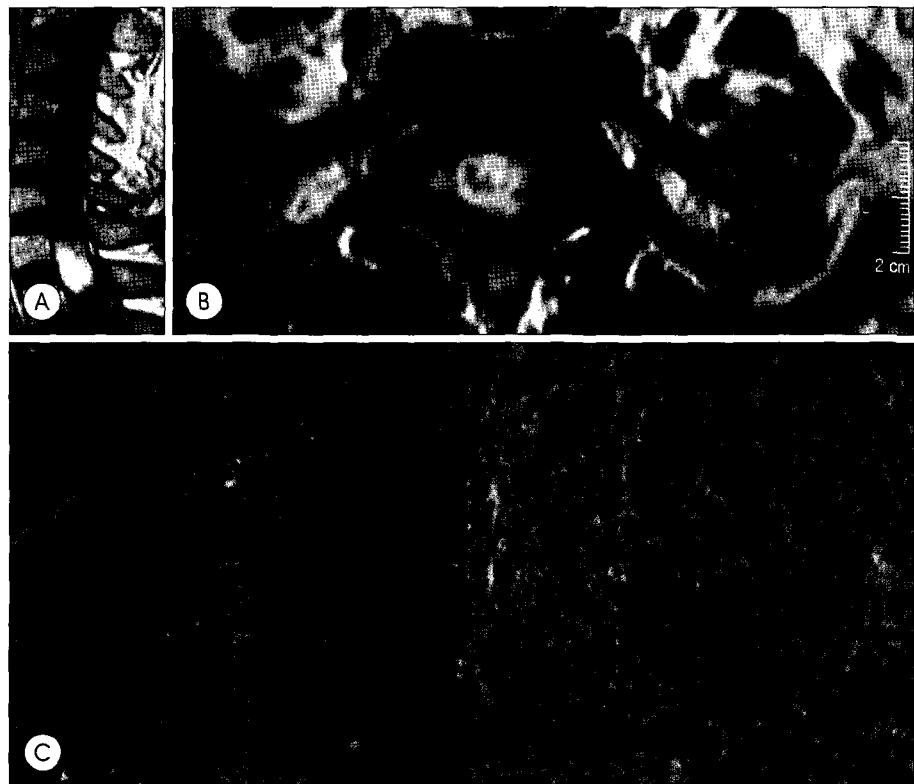
**Table 2.** Presenting symptoms and number of cases

Presenting symptom	Number of cases
pain	6
sensory changes	1
gait disturbance	3
motor weakness	7
voiding difficulty	1

arising from at lumbar 3-4 level, which revealed extradural and foraminal tumor (Fig. 2A, B). In case 4 (NF2), well enhancing intradural-extramedullary lesion at C7-T1 level was demonstrated (Fig. 3A, B). Case 1 (UC) showed intradural-extramedullary lesions at multiple levels (Fig. 4A, B, C, D).

Pathological examination revealed nine cases of neurilemmomas, in one or two more lesions, and eight neurofibromas (including 2 plexiform and 1 myxoid). Unexpectedly, from preoperative MR image indications, meningioma was diagnosed pathologically in case 2.

Immunohistochemical study was performed to investigate the expression patterns of neurofibromin and schwannomin. All of the NF1 cases showed negative staining to anti-NF1 antibody (Ab) and positive staining to anti-Ab (Fig. 2C). Three of four NF2 cases showed positive immunoreactivity

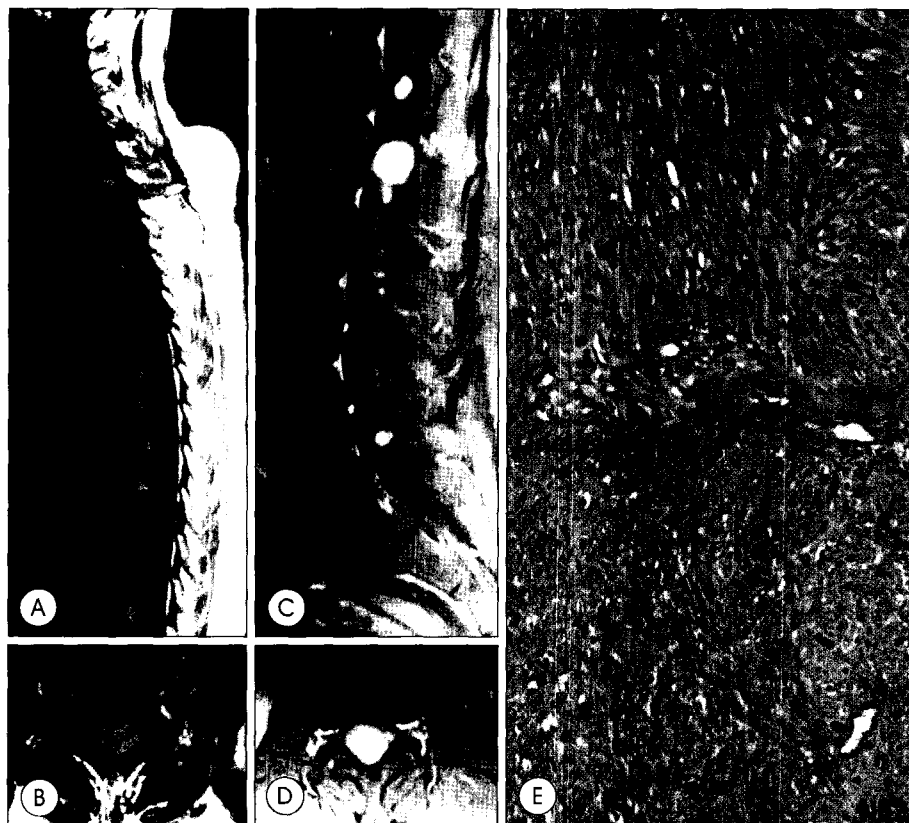


**Fig. 3.** Case 4 (NF2 case). A: Sagittal enhanced T1-weighted magnetic resonance (MR) image, showing enhancing lesions at C7-T1 level and small dot like lesion at T1. B: Axial enhanced T1-weighted MR image, showing an intradural-extramedullary enhancing lesion at C7 level. C: Immunohistochemically, this NF2 case shows strong immunoreactivity to neurofibromin (NF1, Left) (X200), but does not express schwannomin (NF2, Right) (X200).

to anti-NF1 Ab and negative to anti-NF2 Ab (Fig. 3C). One NF2 case (case 2) revealed positive staining to anti-NF1 Ab and weakly positive to anti-NF2 Ab. However, all UC cases showed negative staining to anti-NF1 Ab and positive staining to anti-NF2 Ab, same to NF1 cases (Fig. 4E).

When the clinical, radiological, pathological findings of the three groups were analyzed, preferential location (intradural or extradural) was not observed in cases of NF1 and UC. In cases of UC, the age at presentation was middle-aged to late (mean age 48.5, range 35 to 64), which contrasted with ordinary NF2, where patients tended to become symptomatic before 20 years of age.

Remarkably, UC cases revealed neurilemmoma by pathological examinations and the feature of neurofibromatosis type 1 (negative to anti-NF1 Ab and positive to anti-NF2 Ab) by immunohistochemical study. Although the number of NF2 cases was small, three cases (cases 4, 6, and 18) showed an intraspinal intradural tumor location and two cases (cases 4, and 18) revealed neurilemmoma pathologically. On the other hand, NF1 showed mainly neurofibroma (7 cases) by pathological examination.



**Fig. 4.** Case 1 (UC case). A : A sagittal gadolinium-enhanced spinal magnetic (MR) image, showing three enhancing lesions at C4-T1. B : An axial image at C6, showing intradural extramedullary location of tumor. C : A sagittal gadolinium-enhanced spinal MR image, revealing three enhancing lesions at T12, L1-2, L5. D, An axial image at L1-2, showing intradural extramedullary tumor. E, Immunohistochemically, this UC case revealing immunonegativity to neurofibromin (NF1, Left) (X200), but strong expression of Schwannomin (NF2, Right) (X200).

## Discussion

Because of the extreme clinical heterogeneity of neurofibromatosis, many attempts have been made to classify these disorders into distinct categories, and not surprisingly different classification systems have been suggested by many authors<sup>17,19</sup>. Viskochil et al.<sup>24</sup> in 1992 proposed an alternative classification, which laid the foundation for differentiation by combining clinical and molecular knowledge. They divided the different forms of neurofibromatosis into two broad categories : alternate forms (mixed type, localized type) and related forms. At present, however, the most widely used classification continues to be that recommended in 1987 by the NIH Consensus Conference on Neurofibromatosis<sup>12</sup>. Nonetheless many patients do not fulfill the criteria for NF1 or NF2, and the disease entity of multiple spinal neurogenic tumors, without neurofibromatosis stigmata or a family history, might be represent a form other than neurofibromatosis.

The genetic mechanism of unclassifiable cases according to NIH criteria has been studied by several authors. Somatic mosaicism is a representative mechanism for such phenomenon,

involving localized body segments, unilateral vestibular schwannoma, or incomplete penetrance, etc<sup>18,19</sup>.

Most neurogenic tumors are single sporadic benign neoplasms. A condition characterized by multiple schwannomas was first described in reports from Japan, as neurilemmomatosis or schwannomatosis<sup>16,22</sup>. In the literature, the term schwannomatosis<sup>3,8,11,20</sup> has been used to describe patients with multiple nonvestibular schwannomas with no other sign of NF2. Although it is controversial that schwannomatosis is a variant of NF2, many schwannomas nowadays are classified as a form of NF<sup>20,21</sup>. Jacoby et al.<sup>6</sup> described diagnostic criteria of definite and presumptive schwannomatosis, which accommodated the disease as a form of NF2.

Different forms of familial spinal neurofibromatosis have been reported to show genetic linkage in some families with the NF1 locus, while other cases were thought to

be probably linked to NF2<sup>14,15</sup>). So far, and in one family only<sup>2</sup>), a frameshift mutation (8042nsA) in exon 46 has been detected, which resulted in a truncated NF1 protein. In cases of familial schwannomatosis, the overlap between schwannomatosis and NF2 has been emphasized by the observation that the DNA markers for the NF2 gene segregated with the disease in two large families, in the series of Evans et al.<sup>4</sup>). These authors concluded that schwannomatosis is probably allelic to NF2, with particular mutations predisposing this relatively specific phenotype.

On the other hand, Seppala et al.<sup>21</sup>) found no germline mutations of NF2 gene in seven patients with schwannomatosis. All were middle aged at presentation, in contrast to NF2, in which patients tend to become symptomatic before 20 years of age. They suggested that schwannomatosis differed from NF2.

In our series, in the UC group the age at presentation was also during late middle age. In the literature, spinal tumors in NF1 are primarily intraforaminal, extending into the spinal canal (extraspinal), while in NF2 they are mostly intraspinal tumors<sup>10,23</sup>). In our cases, three of four NF2 cases showed such a pattern, especially an intradural location. However, NF1 and UC cases showed diverse spinal locations.

In general, spinal tumors in patients with NF1 are neurofibroma, and in patients with NF2 they are schwannomas<sup>5</sup>). In our series, meningioma was confirmed pathologically, in case 2, as an NF2. There are several possible explanations for the presence of meningioma tissue in a schwann cell tumor, including; divergent differentiation from a common cell line, metaplasia in a typical schwannoma, entrapment of hyperplastic arachnoidal cells, and a collision of separate tumors in which two contiguous neoplasms merge into one<sup>13</sup>).

In our series, all the UC cases and three of the four NF2 cases showed neurilemmoma on pathological examination. On the other hand, NF1 showed mostly neurofibroma. Although the number of our cases is small, UC cases might be included in a different syndrome from usual neurofibromatosis, as they have no family history and no neurofibromatosis stigmata, though they showed multiple spinal tumors, which were mostly neurilemmomas like NF2. However, immunohistochemically, the UC group showed similarity to NF1 group. Therefore, the authors suggest that UC cases might share some characteristics of both NF1 and NF2 or could be classified as a different neurofibromatosis type, though they showed immunoreactivity of NF1.

## Conclusion

**M**ultiple neurogenic tumors in the spinal canal could be an under-recognized disease entity. Clinically,

though all of the resected tumors were benign, close observation is necessary for multiple spinal neurogenic tumors. Although further studies to identify genetic aberrations in this disease entity are needed, the multiple neurogenic tumors in the spinal canal which is unclassifiable by the NIH classification may be a different neurofibromatosis type that show some common characteristics of both NF1 and NF2.

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