Original article

Schwannomatosis: a new member of neurofibromatosis family

CHEN Shan-lin, LIU Chang, LIU Bo, YI Chuan-jun, WANG Zhi-xin, RONG Yan-bo, ZHU Jin, DING Yi and TIAN Guang-lei

Keywords: *schwannomatosis; neurofibromatosis 2; nervous system neoplasm; magnetic resonance imaging*

Background Schwannomatosis is a recently recognized peripheral nerve polyneoplasm with clinical characteristics and a genetic background that differ from those of neurofibromatosis 2 (NF2). The diagnostic and treatment criteria of this rare disorder are herein discussed.

Methods The data of 180 patients who underwent operations for benign schwannomas from 2003 to 2012 in our center were reviewed. Eight of them were classified as schwannomatosis according to the diagnostic criteria suggested by MacCollin. The demographic characteristics were documented and compared between the two groups of patients. The patients' clinical presentations, imaging characteristics, histological features, and treatment results were retrospectively investigated and summarized.

Results Of the 180 cases of benign schwannomas we reviewed this time, eight patients presented with schwannomatosis (4.44%). The mean age of the two groups was not significantly different (40.0 vs. 44.7 years, t=0.88, P=0.378). However, schwannnomatosis seems to more generally occur in females (75% vs. 48% were females, P=0.162), although the difference was not statistically significant. The initial main symptom was pain. The neurological examination was otherwise normal. Magnetic resonance imaging (MRI) revealed multiple discrete, well-defined round, or oval lesions distributed along the course of the peripheral nerves in the extremities with low-to-intermediate signal intensity on T1-weighted images and high-signal intensity on T2-weighted images. Vestibular schwannomas were excluded in four patients by cranial MRI. The lesions in all patients were resected and were pathologically proven to be schwannomas. The average follow-up period was 26 months. Six individuals obtained a good result without symptoms or function loss.

Conclusions Schwannomatosis is characterized by the development of multiple schwannomas without evidence of the vestibular tumors that are diagnostic for NF2. It commonly occurs in middle-aged females. It has similar demographic features to solitary benign schwannoma. Surgical resection always results in a good outcome.

Chin Med J 2013;126 (14): 2656-2660

Schwannomas are the most common benign nerve sheath tumors originating in Schwann cells. They usually exist as solitary encapsulated masses in otherwise normal individuals and have no sex predilection. However, they occasionally occur as multiple tumors, which suggests an underlying tumor predisposition syndrome.[1] The most common such syndrome is neurofibromatosis 2 (NF2), the hallmark of which is bilateral vestibular nerve schwannomas (Figure 1). It was recently recognized that some patients with multiple schwannomas lack vestibular tumors. This condition constitutes the third major form of neurofibromatosis, termed schwannomatosis.[2,3]

There have been several clinical reports of multiple schwannomas since 1996.[2-6] Based on these reports and concomitant genetic research, schwannomatosis has been deemed a clinical entity different from other forms of neurofibromatosis and associated with specific diagnostic criteria[4] (Table 1).

The low incidence of schwannomatosis contributes to the difficulty in obtaining an accurate diagnosis.[7] We investigated the characteristics of patients with schwannomatosis diagnosed according to the MacCollin criteria. We also analyzed the data from the clinical appearance, imaging, and histopathological features of these cases and finally summarized the treatment principle.

METHODS

Patients

A total of 314 patients with benign schwannomas underwent operations at Beijing Jishuitan Hospital from 2003 to 2012. Among them, we reviewed the data of 180 patients treated in the Hand Surgery Department. Eight of these 180 patients had multiple pathologically confirmed schwannomas without evidence of the vestibular schwannomas that are diagnostic for NF2. No patients in this group had other signs of neurofibromatosis 1 (NF1). All patients were determined to have schwannomatosis according to the diagnostic criteria provided by MacCollin and colleagues (Table 1).

Clinical data

Six individuals were examined by one of the authors in the

DOI: 10.3760/cma.j.issn.0366-6999.20130615

Department of Hand Surgery (Chen SL, Liu C, Liu B, Yi CJ, Wang ZX, Rong YB, Zhu J and Tian GL), Department of Pathology (Ding Y), Beijing Jishuitan Hospital, Beijing 100035, China

Correspondence to: Dr. TIAN Guang-lei, Department of Hand Surgery, Beijing Jishuitan Hospital, Beijing 100035, China (Fax: 86-10-58516095. Email: tiangl57@163.com)

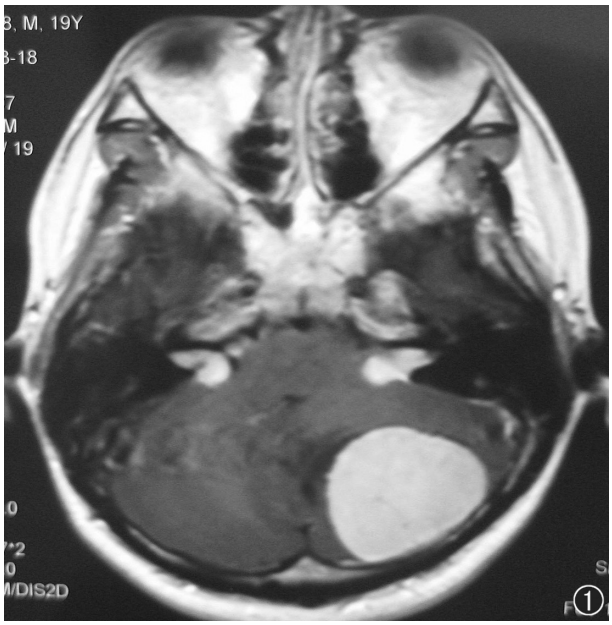

Figure 1. A 19 years old man presented with multiple neural tumors along the radial nerve in his right arm. Because a pathological reflex was elicited, cranial MRI was performed to exclude NF2. MRI revealed eight bilateral nerve masses and a meningioma. He was finally diagnosed with NF2.

Table 1. Proposed diagnostic criteria for schwannomatosis[4]

Types	Description
Definite schwannomatosis	Age >30 years and two or more non-intradermal schwannomas (at least one with histological confirmation). No evidence of vestibular tumor on MRI scan AND no known constitutional mutation. OR one schwannoma confirmed with histology and a first-degree relative who meets the above criteria.
Possible schwannomatosis	Age <30 years and two or more non-intradermal schwannomas (at least one with histological confirmation). No evidence of vestibular tumor on MRI scan AND no known constitutional mutation. Age >45 years and no symptoms of eighth nerve dysfunction and two or more non-intradermal schwannomas (at least one with histological confirmation). Radiographic evidence of a schwannoma and a first-degree relative who meets the criteria for definite schwannomatosis.
Segmental schwannomatosis	Meets criteria for definite or possible schwannomatosis but limited to one limb or five or fewer contiguous segments of the spine.

hand injury clinic at the Beijing Jishuitan Hospital. The other two patients were identified because of mass recurrence (one patient), and peripheral nerve injury (one patient) NF1 was determined from the postoperative examination in the other hospital. In each case, we retrospectively analyzed patient's sex and age and reviewed the medical, surgical, radiologic, and pathologic records of the patient with specific attention to the location and size of the tumors, other signs of NF1, results of ophthalmologic evaluation, and family history. Histopathological examinations of all available surgical specimens were conducted. The clinical features of all patients are summarized in Table 2.

Statistical analysis

The demographic characteristics were documented and compared between the eight patients and the other 172 patients. The difference of quantitative data was detected by two independent samples *t*-test and qualitative data were compared using Fisher's exact test. For all analyses, two-sided *P* values of less than 0.05 were considered significant. All analyses were conducted using SPSS version 18.0 (SPSS Inc., USA).

Case reports

Patient 1

A 54 years old woman (Patient 2 in Table 2) had a 3-month history of painful masses in the bilateral popliteal fossae. She underwent resection of the right adrenal adenoma associated with Cushing's syndrome 1 year previously. Physical examination revealed no other cutaneous evidence of NF1 or NF2 and no neurologic abnormalities. Magnetic resonance imaging (MRI) of the popliteal region revealed a left-sided subcutaneous mass in close approximation to the cutaneous nerve and a deep right-sided subcutaneous mass seated near the common fibular nerve. The tumors were of low-signal intensity on T1-weighted images, similar to the intensity of muscle tissues, and the tumors were of uneven high-signal intensity on T2-weighted images. During the operation, we found that the left tumor originated from the sural nerve and that the right tumor originated from the common fibular nerve. One small tumor was found in the branches of the sural nerve that had not been revealed by MRI. The tumors were encapsulated masses with a dark yellow color. They were well defined and could be completely removed. All three tumors were pathologically diagnosed as schwannomas (Figure 2).

Patient 2

A 28 years old woman presented with many painless masses of different sizes in her left forearm. The masses had gradually enlarged during the previous 3 years. On physical examination, there were no cutaneous signs of NF1 and no evidence of NF2. Numbness was elicited and irradiated to the web space when some of the masses were tapped. The MRI results suggested the presence of multiple neural tumors. Surgical exploration revealed six tumors in the left forearm and hand. The tumors involved the radial nerve and the median nerve. They were light yellow and had smooth surfaces. All of the tumors were encapsulated and well defined and could be completely removed. Four tumors were selected for pathological diagnosis, and all were confirmed to be benign schwannomas (Figure 3).

RESULTS

Baseline characteristics

Of the 180 cases of benign schwannomas we reviewed this time, eight patients presented with schwannomatosis (4.44%). After the comparison between the eight patients and the other 172 individuals, the mean age of the two groups was not significantly different (40.0 vs. 44.7 years, *t* value=0.88, *P*=0.378). However, schwannnomatosis seems to more generally occur in females (75% vs. 48% were females, *P*=0.162), although the difference was not statistically significant.

Table 2. Clinical characteristics of patients with schwannomatosis

Patient	Age (yr)	Age onset	Sex	Initial symptoms	Distribution of tumors	Nerves involved	Family history	Tumor removed	Pathological result	FU (mos)
1	35	34	F	Pain and mass	L arm and thigh	RN and saphenous nerve	None	2	Sch	36
2	54	54	F	Pain and mass	Bilateral popliteal space	Common fibular nerve and SN	None	2	Sch	20
3	42	40	F	Pain and mass	Bilateral popliteal space L calf, and foot	L SN R Common fibular nerve and SN	None	3 (8 altogether)	Sch	18
4	48	32	M	Pain	R hand and wrist	MN and UN	None	7	Sch	36
5	35	26	F	Pain	R hand	MN and UN	One sister with suspected NF1	9	Sch	50
6	42	41	F	Numbness and mass	L forearm and ring finger	UN and digital nerve	None	2	Sch	17
7	28	24	F	Mass	L forearm and hand	RN and MN	None	6	Sch	8
8	35	25	F	Pain	R hand	RN and MN	None	2	Sch	24

Nerves involved were given by surgery. yr: years; FU: follow-up; mos: months; F: female; M: male; L: left; R: right; RN: radial nerve; MN: median nerve; UN: ulnar nerve; SN: sural nerve; Sch: schwannoma.

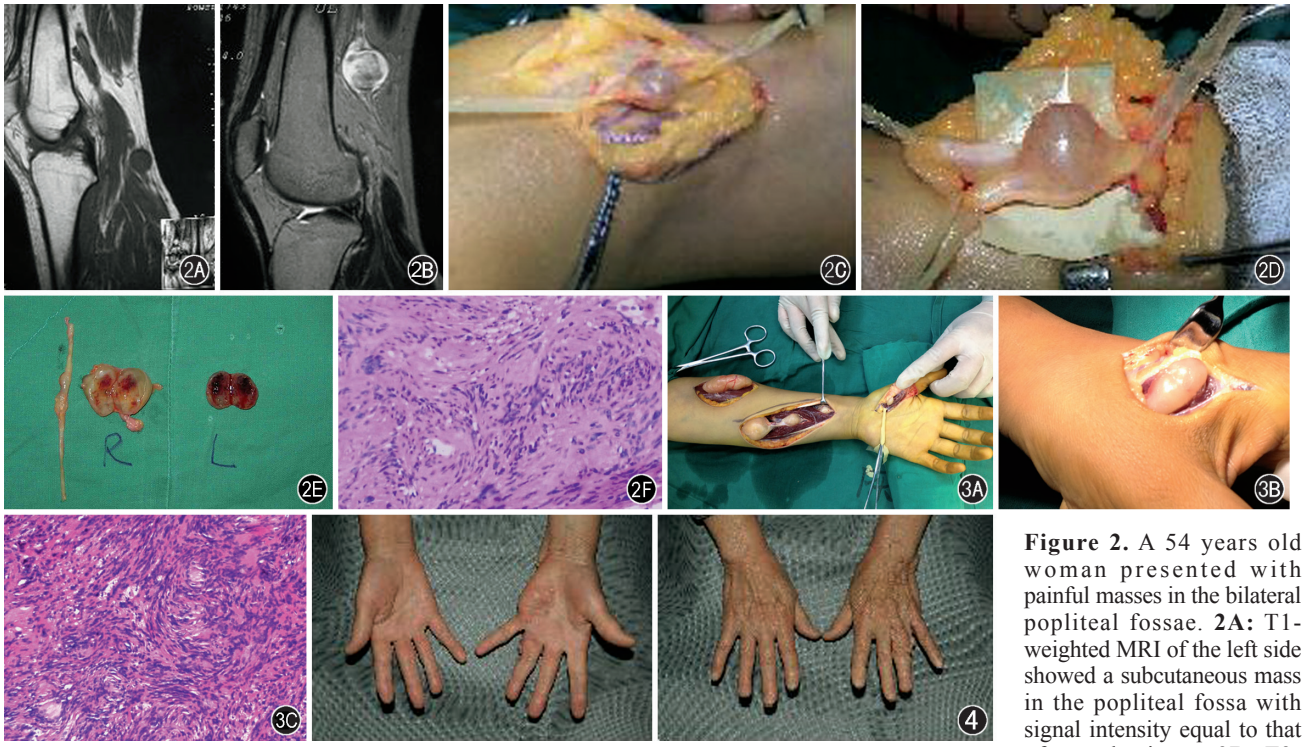

Figure 2. A 54 years old woman presented with painful masses in the bilateral popliteal fossae. **2A:** T1-weighted MRI of the left side showed a subcutaneous mass in the popliteal fossa with signal intensity equal to that of muscle tissue. **2B:** T2-weighted image of the right side revealed a round mass seated deeply along the nerve with high-signal intensity and a target sign. **2C:** The left tumor was located at the sural nerve. **2D:** The right tumor was located at the common fibular nerve. **2E:** Three tumors were enucleated leree tumros ere enucuular nerve during the operation. **2F:** The pathologically defining feature was the pattern of alternating Antoni A and Antoni B areas; the diagnosis was benign schwannoma (HE, original magnification ×200).

Figure 3. This 28 years old female patient presented with a 4-year history of painless masses in the left forearm and hand. Six tumors of various sizes were found during the surgical exploration. They were located at the forearm thenar eminence **3A:** 4 angnosis, the result were shwae, and first web space; **3B:** involved the radial nerve and median nerve separately. Four tumors were selected for pathological diagnosis, and the results were consistent with benign schwannoma with typical manifestations (HE, original magnification ×200) (**3C**).

Figure 4. Segmental neurofibromatosis on the left hand of a 52 years old female patient.

Seven of them were female and one was male. The average age among these patients was 40 years (range, 28–54 years) at the time of the operation. One patient (Patient 2 in Table 2) reported that she had undergone adrenal tumor resection because of Cushing's syndrome 1 year previously. One individual (Patient 5 in Table 2) has a sister with suspected NF1. No other patients had a family history of multiple neural tumors.

Symoptoms

The initial symptom was pain in six patients, and this pain gradually became disabling in four patients. The tumors were consistently described as eliciting shooting pain or paresthesia in the extremity at the control area of the peripheral nerves when the masses were tapped. The other two patients had painless palpable masses, and their disease was found incidentally. No café au lait spots or axillary freckling was noted. The neurological examination was otherwise normal.

Two patients (Patients 2 and 3 in Table 2) had bilateral popliteal tumors. The other six patients (75%) had segmental schwannomatosis involving multiple tumors limited to one side of the trunk, five in whom the disease

was limited to an upper extremity (62.5%).

Preoperative MRI of the extremities in seven patients showed that the masses were well-defined round or oval lesions distributed along the course of the peripheral nerves in the extremities. They were of low-signal intensity on T1-weighted images, similar to the density of muscle tissues, and they were of uneven high-signal intensity on T2-weighted images. A target appearance was seen in four of these patients. In four patients, cranial MRI revealed no evidence of vestibular schwannomas.

Surgical treatment outcome

All eight patients underwent surgical resection. The tumors were encapsulated, well circumscribed, and located at the common peroneal nerve, sural nerve, radial nerve, saphenous nerve, median nerve, ulnar nerve, radial nerve, and digital nerve, respectively. The main pathological manifestation was the pattern of alternating Antoni A areas, which had highly ordered cellular components, and Antoni B areas, which were far less ordered and less cellular; this alternating pattern is the hallmark of benign schwannomas.

Follow-up results

The mean postoperative follow-up period was 26 months (8–50 months). The pain disappeared in five patients with painful tumors and decreased in one patient. There was no noticeable loss of function in seven patients postoperatively. No recurrence occurred with the exception of one patient whose palmar tumor recurred (Patient 5 in Table 2).

In one patient (Patient 3 in Table 2), bilateral popliteal tumors were misdiagnosed as Baker's cysts. After resection of the "cysts" at a local hospital, she lost the capability to extend her ankle joints bilaterally. She was then referred to our center and underwent sural nerve grafting and resection of the remaining tumors. She had not achieved functional recovery 20 months after the operation.

DISCUSSION

The schwannoma is the most common nerve sheath tumor. It occurs as a solitary mass in genetically normal individuals. Multiple schwannomas are most commonly associated with NF2, which is characterized by bilateral vestibulocochlear nerve tumors. Without this hallmark, the presence of multiple schwannomas is termed schwannomatosis.

In 1996, MacCollin et al[3] reported 14 patients who developed multiple pathologically defined schwannomas without vestibular schwannomas.[3] They suggested that schwannomatosis should be considered as a clinical entity distinct from NF2. In 1997, they developed the first proposed diagnostic criteria for this disease.[5] Since then, increasing numbers of authors have gradually accepted the conclusion that schwannomatosis is clinically distinct from NF2 on account of several lines of evidence: (1) NF2 develops because of a germline mutation on chromosome 22q12,[7-9] but the etiology of schwannomatosis is unexplained. Sestini et al[10] and Hadfield et al[11] considered that a germline mutation of *SMARCB1*, the tumor suppressor gene located not far from chromosome 22q12, is closely related to the disease. (2) NF2 is characterized by bilateral vestibular schwannomas and symptoms appear at a relatively young age. The main complaints include deafness, tinnitus, instability, vertigo, and vestibular nerve symptoms. Schwannomatosis does not affect the bilateral vestibular nerves and most commonly occurs at 30–60 years of age. Pain or paresthesia may occur, but the neurological examination is otherwise normal. (3) Patients with schwannomatosis usually present with pain,[3] and patients with NF2 usually present with dysfunction.

Based on the criteria proposed by MacCollin et al,[4] four individuals in this series were definitively diagnosed with schwannomatosis after performing MRI to rule out vestibular tumors. The other four patients had possible schwannomatosis. Six of the eight patients were diagnosed with segmental schwannomatosis.

Four surgical series reported that schwannomatosis occurred in 2.4%–5.0% of patients with schwannomas.[12-15] These findings are consistent with the results of our series, in which schwannomatosis occurred in 4.44% of patients with benign schwannomas. According to the literature, familial schwannomatosis is present in fewer than 20% of patients with schwannomatosis,[2-4,12] and approximately one-third of reported cases of schwannomatosis are anatomically localized to a single limb or segment of the spine.[14,16,17] However, only one patient had a questionable history of familial schwannomatosis in this series. Conversely, there was a higher proportion of patients with segmental schwannomatosis (75%) in this series. Furthermore, the disease was limited to an upper extremity in five individuals (62.5%). The low proportion of patients with familial schwannomatosis and high proportion of patients with segmental schwannomatosis can be partly explained by the fact that as a hand surgery center, most of the neural tumors we manage are those that occur in all four extremities, especially the upper extremities. Another probable reason for the data bias is that almost half of the patients with schwannomas (n=141) were treated in the oncology department of Jishuitan Hospital, none of whom were included in this study.

The development of multiple schwannomas has a female predilection, Which is contrary to the conclusions of other studies, which documented that schwannomatosis affects men and women equally. There is no reasonable explanation for this discrepancy.

The average patient age in this group was 39.6 years, which is in accordance with MacCollin's opinion that "many individuals with schwannomatosis present symptoms in the fourth or fifth decade.[4]" It is indicated that schwannomatosis is a different entity from NF2 because it is well past the average age at onset of hearing loss in NF2

in the second decade.

Multiple palpable masses with rest pain are the main problem confronting patients with schwannomatosis. The most common finding is shooting pain or paresthesia elicited when tapping the masses at the control area of the involved peripheral nerve. The typical imaging and histopathological findings of schwannomatosis are identical to those of solitary schwannomas.

There are several kinds of multiple soft tissue masses in the four extremities that must be carefully differentiated from schwannomatosis, such as segmental NF1 (Figure 4) and multiple lipomas. The symptoms of segmental NF1 are identical to those of segmental schwannomatosis; however, both tumors are more superficial and are associated with café au lait spots, which can help to achieve an accurate diagnosis. The histopathological manifestations differ and are used to confirm the diagnosis. Multiple lipomas are painless, movable soft tissue tumors that propagate on the trunks and four extremities. Sonography and MRI can be used to easily establish the correct diagnosis.

The indications for schwannoma excision in patients with schwannomatosis follow the same principles as those guiding the management of solitary schwannomas. Excision of painful tumors can provide a satisfactory result with a low recurrence rate. Gonzalvo et al[1] reported two malignant schwannomas in one family in his series. His finding challenges the concept that schwannomatosis occurs only as benign tumors. However, the result of the present series showed that there was no tendency toward malignant changes during the follow-up period. The presumptive explanation of this discrepancy is the same as that mentioned above.

The limitation of our study is the lack of molecular testing in all of our patients. The molecular background of schwannomatosis remains unclear. In 1997, Jacoby et al[5] found a mosaic alteration of the NF2 gene mutation. However, they also suggested that a non-NF2 locus was implicated in some patients. The *CABINI* gene, localized on the same chromosome as NF2 (chromosome 22) but centromeric to it, has been implicated in the pathogenesis of both NF2 and schwannomatosis.[18] Neither molecular genetic testing nor prenatal diagnosis is currently available for schwannomatosis,[4] and the final, most definitive diagnostic modality will be the identification of the schwannomatosis locus itself.

REFERENCES

1. Gonzalvo A, Fowler A, Cook RJ, Little NS, Wheeler H, MacDonald K, et al. Schwannomatosis, sporadic schwannomatosis, and familial schwannomatosis: a surgical series with long-term follow-up. J Neurosurg 2011; 114: 756-762.
2. Baser ME, Freidman JM, Evans DG. Increasing the specificity of diagnostic criteria for schwannomatosis. Neurogenetics 2006; 66: 730-732.
3. MacCollin M, Woodfin W, Kronn D, Short MP. Schwannomatosis: a clinical and pathologic study. Neurology 1996; 46: 1072-1079.
4. MacCollin M, Chiocca EA, Evans DG, Friedman JM, Horvitz R, Jaramillo D, et al. Diagnostic criteria for schwannomatosis. Neurology 2005; 64: 1838-1845.
5. Jacoby LB, Jones D, Davis K, Kronn D, Short MP, Gusella J, et al. Molecular analysis of the NF2 tumor suppressor gene in schwannomatosis. Am J Hum Genet 1997; 61: 1293-1302.
6. Antinheimo J, Sankila R, Carpen O, Pukkala E, Sainio M, Jaaskelainen J. Population-based analysis of sporadic and type 2 neurofibromatosis-associated meningiomas and schwannomas. Neurology 2000; 54: 71-76.
7. Trofatter J, MacCollin M, Rutter JL, Murrell JR, Duyao MP, Parry DM, et al. A novel moesin-esrin-radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. Cell 1993; 72: 791-800.
8. Roleau G, Merel P, Lctchman M, Sanson M, Zucman J, Marineau C, et al. Alteration in a new gene encoding a putative membrane-organising protein causes neurofibromatosis 2. Nature 1993; 363: 515-521.
9. Ferner R. Neurofibromatosis 1 and neurofibromatosis 2: a twenty first century perspective. Lancet Neurol 2007; 6: 340-351.
10. Sestini R, Bacci C, Provenzano A, Genuardi M, Papi L. Evidence of a four-hit mechanism involving SMARCB1 and NF2 in schwannomatosis-associated schwannomas. Hum Muta 2008; 29: 227-231.
11. Hadfield KD, Newman WG, Bowers NL, Wallace A, Bolger C, Colley A, et al. Molecular characterisation of SMARCB1 and NF2 in familial and sporadic schwannomatosis. J Med Genet 2008; 45: 332-339.
12. Antinheimo J, Sankila R, Carpen O, Pukkala E, Sainio M, Jaaskelainen J. Population-based analysis of sporadic and type 2 neurofibromatosis-associated meningiomas and shwannomas. Neurology 2000; 54: 71-76.
13. Seppala MT, Sainio Ma, Haltia MJ, Kinnenen JJ, Setala KH, Jaaskelainen JE. Multiple schwannomas: schwannomatosis or neurofibromatosis type 2? J Neurosurg 1998; 89: 36-41.
14. Ogose A, Hotta T, Morita T, Morita T, Otsuka H, Hirata Y. Multiple schwannomas in the peripheral nerves. J Bone Joint Surg Br 1998; 80: 657-661.
15. Huang JH, Simon SL, Nagpal S, Nelson PT, Zager EL. Management of patients with schwannomatosis: report of six cases and review of the literature. Surg Neurol 2004; 62: 353-361.
16. Kaufman Dl, Heinrich BS, Willett C, Perry A, Finseth F, Sobel RA. Somatic instability of the NF2 gene in schwannomatosis. Arch Neuro 2003; 60: 1317-1320.
17. Leverkus M, Kluwe L, Roll Em, Becker G, Brocker EB, Mauthner VF, et al. Multiple unilateral schwannomas: segmental neurofibromatosis 2 or schwannomatosis? Br J Dermatol 2003; 148: 804-809.
18. Buckley PG, Mantrioragada KK, Diaz de Stahl T, Piotrowski A, Hansson CM, Kiss H, et al. Identification of genetic aberrations on chromosome 22 outside the NF2 locus in schwnnomatosis and neurofibromatosis type 2. Hum Mutat 2005; 26: 540-549.

(Received March 4, 2013)
Edited by HAO Xiu-yuan