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Plexiform neurilemoma: a clinicopathological and immunohistochemical analysis of 23 tumours from 20 patients

Toshimitsu Iwashita and Munetomo Enjoji

Second Department of Pathology, Faculty of Medicine, Kyushu University, 60,3-1-1 Maidashi, Higashi-ku, Fukuoka 812, Japan

Summary. A clinicopathological and immunohistochemical study was done on 23 plexiform (multinodular) neurilemomas excised from 20 Japanese. Ages of the subjects ranged from 2 years to 69 years with a mean age of 30 years. The tumours occurred most often on the trunk (14), and were located commonly in the dermis and subcutis (19). Three lesions apparently originated from the peripheral nerve trunks. Multiple tumours were observed in six instances, and two were associated with von Recklinghausen's disease. Microscopically, they appeared as multinodular growths, most nodules were moderately cellular, and both Antoni A and B patterns were distinct in 10 tumours. Obvious Verocay bodies were noted in seven tumours and abortive ones in five. Immunohistochemical reactivity to S-100 protein was demonstrated in both nuclei and cytoplasm of almost all tumour cells of all lesions examined. Recurrences are nil among the 4 patients who could be followed. Correlations with trauma and with von Recklinghausen's disease are briefly discussed.

Key words: Peripheral nerve sheath tumour – Plexiform neurilemoma – S-100 protein

Introduction

Masson seems to have been the first to report data on two patients with plexiform schwannogliosis, one of them with von Recklinghausen's disease. Thereafter, this tumour was reported only sporadically (Barbosa and Hansen 1984; Enzinger and Weiss 1983; Kleinman et al. 1985; Woodruff et al. 1983) except for Harkin et al. who presented six cases under the name "benign plexiform schwannoma" at the Eighth International Congress of Neuropathology in 1978. Fletcher and Davies (1986) reported data on seven patients with this rare condition. The current terminology for this tumour is based on the description by Enzinger and Weiss (1983) who wrote that plexiform neurilemoma was a rare soft-tissue neoplasm and had been confused with plexiform neurofibroma.

We now report findings on 23 plexiform neurilemomas excised from 20 patients. The immunohistochemical reactivities to S-100 protein and several other neurogenic markers are described.

Offprint requests to: M. Enjoji at the above address

Materials and methods

The materials used in this study were selected from among approximately 19000 cases of soft tissue tumours filed in our laboratory during the period 1956–1985, in which 1057 with neurilemomas of soft parts were included. Twenty-one plexiform tumours in 18 patients were selected from the 1057 cases and two others from consultation cases were added, making a total of 23 tumours from 20 patients.

All microscopic sections had been stained with haematoxylin and eosin. In all but three tumours, the following additional special stains were used: periodic acid-Schiff (PAS), Alcian blue, Masson's trichrome, Bodian's stain for neurofibrils, Klüver-Barrera for myelin, and silver impregnation for reticulin. Fontana-Masson stain was used for one case of pigmented tumour.

Four-micron-thick sections of 10% formalin-fixed, paraffin-embedded materials from 20 lesions in 17 cases of plexiform neurilemoma were stained for several immunohistochemical products such as S-100 protein, glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), neurone specific enolase (NSE) and neurofilament. These sections were incubated overnight at 4° C with primary antibody at the indicated dilutions: rabbit anti-bovine-S-100 protein serum (kindly provided by Dr. T. Nakajima (1982), National Cancer Center Research Institute, Tokyo, Japan), 1/1000; rabbit anti-GFAP (DAKO-immunoglobulins Ltd, Copenhagen, Denmark), 1/200; rabbit anti-MBP (DAKO, Copenhagen, Denmark), 1/200; rabbit anti-NSE (kindly provided by Dr. M. Kuramitsu (1986), Department of Neuropathology, Neurological Institute, Faculty of Medicine, Kyushu University, Fukuoka, Japan), 1/1000; mouse anti-neu-

rofilament (Labsystems, Helsinki, Finland), 1/100. Locations of the above antigens were demonstrated by the avidin-biotin-peroxidase complex method of Hsu et al. (1981).

Results

Clinical findings

Clinical data of the 20 Japanese patients are given in Table 1. There were 8 males and 12 females, their ages ranging from 2 years to 69 years with a mean age of 30 years (median 30 years); 80% of the patients were under 40.

Of the 23 tumours, 14 were located on the trunk, six in the upper extremities, two in the head and one in the lower extremities. Dermal or subcutaneous locations were evident in 19 of the 23 tumours and three of the four deep-seated tumours showed a close anatomical relationship to discernible peripheral nerves; the intercostal, ulnar and posterior occipital nerves, respectively.

Tumour formation with its gradual increase in size was almost always one of the main clinical signs. Spontaneous pain occurred in three, tenderness in four and radiating pain in one. The duration of symptoms before treatment ranged from one month to 30 years with a mean of eight years (median seven years). Multicentricity of the tumours was observed in six instances; two tumours in each of three patients and more than three lesions in each of three others. Two patients had been clinically diagnosed as cases of von Recklinghausen's disease. One of these patients had multiple skin tumours with no pigmentation and the other a pigmented macula in the right thigh, measuring 2 cm in diameter, and tumours of both acoustic nerves and thoracic and lumbar spinal nerves. However, these tumours had not been examined histologically for neurofibromatosis. In no patient was there a history of trauma at the tumour site.

Pathological findings

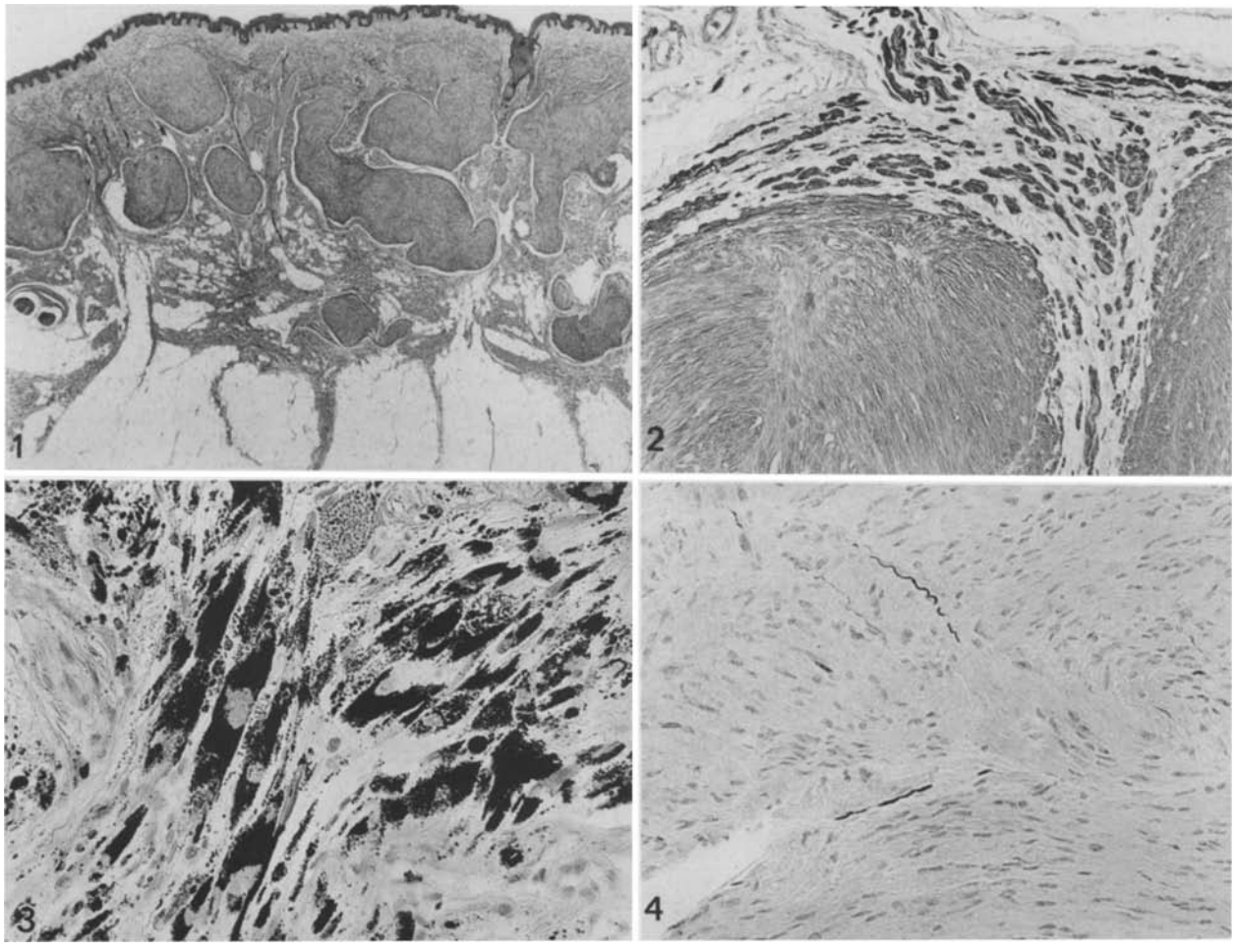
The sizes of tumours at the time of surgical excision ranged from 0.5 cm to 7 cm with a mean of 2.4 cm (median 1.9 cm) in the greatest diameter. Thirteen were located within the dermis, six in the subcutaneous tissue and four in the deep soft tissue. The tumours were well demarcated in five and poorly circumscribed in two and were described as hard or elastic hard in consistency in six and elastic soft in one. The cut surfaces were usually yellowish white.

Histologically, the tumours were made up of multiple nodules of varying sizes, were interconnected and were embedded in fibrous connective tissue (Fig. 1). Each nodule was surrounded by a thin or slightly thicker fibrous capsule, occasionally admixed with the residual depressed nerve fibers (Fig. 2). Most nodules were moderately cellular, but in three, the nodules retained a higher cellularity. Tumour cells bore elongated nuclei and a weakly eosinophilic fibrillary cytoplasm with no apparent cell borders. Mitoses were rare (less than 2/20 HPF) and no necrosis was seen except for one case showing infarction. Nuclear palisades were evident in 19 of the 23 tumours, distinct Verocay bodies in seven and abortive ones in five. Although most tumours were mainly composed of the compact cellular component (Antoni A area), both Antoni A and B patterns were discriminated in 10 tumours. In one tumour, each nodule mainly consisted of a myxoid Antoni B area. Neurofibroma-like patterns characterized by wavy bands of collagen and tortuous spindle cells in a myxoid background were present to some extent in four tumours. Three were cellular, deeply located and originated from the ulnar nerve in one instance and from the posterior occipital nerve in another. Degenerative changes, including perivascular hyalinization and cyst formation within the tumour were found in only one. Melanin pigment, confirmed by Fontana-Masson stain, was present in many tumour cells of one case (Fig. 3), but was not found in others. Alcian blue for acid mucopolysaccharides stained the peripheral myxoid areas of the nodules in 20 lesions, the stainability appearing to be identical with that in the normal peripheral nerves. Both Bodian and Klüver-Barrera failed to demonstrate either nerve fibers or myelin sheaths within the tumours.

Immunohistochemical studies were performed on 20 lesions from 17 patients. In all 20 tumours examined, the cells were distinctly positive for S-

Table 1. Clinical summary of 23 tumours in 20 patients with plexiform neurilemomas

Age	2–69 years (average 30 years)
Sex	M:F = 8:12
Location	
Head	2
Trunk	14 (Back 4, Flank 3, Chest 3, Buttock 1, Waist 1, Inguinal 1, Abdomen 1)
Upper extremities	6 (Upper arm 1, Forearm 2, Hand 3)
Lower extremities	1 (Thigh 1)
Size of Tumour	0.5–7 cm (average 2.4 cm)
Duration	1 mo.–30 years (average 8 years)
Age of Onset	2 yrs.–58 years (average 19 years)



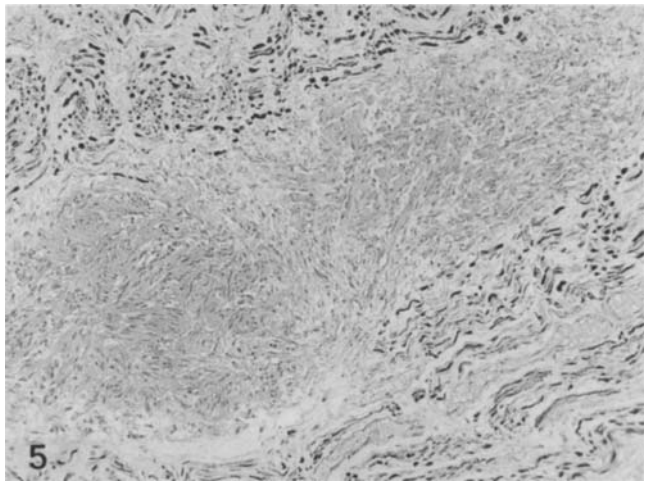


Fig. 1. Dermal tumour showing a plexiform (multinodular) growth. Nodules vary in size and interconnect. (× 10.4)

Fig. 2. Tumour nodules consisting of S-100 protein immunoreactive tumour cells surrounded by residual nerve fibers which are more strongly immunoreactive to S-100 (ABC method). (× 155)

Fig. 3. Melanin pigment granules in the neoplastic Schwann cells demonstrated by Fontana-Masson stain. (× 320)

Fig. 4. A few linear or spiral axons in the tumour evidenced by immunohistochemical stain for neurofilament. (× 208)

Fig. 5. Intraneural tumour growth as shown by immunohistochemical stain for neurofilament. The tumour is situated in the center of the nerve which stained strongly for neurofilament. (× 104)

100 protein with a slightly weaker intensity of immunostaining than in the normal peripheral nerves. The more intensely stained normal nerves were found in the peripheral or septal areas of the nodules, suggesting intraneural growth of the tumours (Fig. 2). The distinct immunoreactivity to S-100 protein was recognized in both the nuclei and the cytoplasm of almost all tumour cells (Fig. 2). Sixteen tumours showed a weak immunoreactivity for GFAP and the remaining four stained negative for this protein. None of the 20 tumours carried any immunoreactivity to MBP, in distinct contrast with the normal peripheral nerves. NSE was weakly positive in all 20 tumours,

Table 2. Reported cases of plexiform neurilemomas

Year	Author(s)	Age	Sex	Location
Before	Masson (two cases)	Not given	Not given	Cutaneous
1956		Not given	F	Clitoris
1978	Harkin et al. (six cases)	9–39 years	Not given	Not given
1983	Woodruff et al.	26 years	F	Vulva
1983	Enzinger et al.	Not given	Not given	Not given
1984	Barbosa et al. (three cases)	12–36 years (average 23 years)	M:F=2:1	Head 3
1985	Kleinman et al.	33 years	M	Index finger
1986	Fletcher et al. (seven cases)	22–71 years (average 37 years)	M:F=4:3	Head & Neck 4; Trunk 3

and the neurofilament antigen made visualization of the nerve fibers feasible within the tumours in all 20; for the peripheral areas in 13 and for the middle portions in 18 (Figs. 4 and 5).

Prognosis

Of four patients who could be followed, three are well without recurrence, the follow-up period ranging from two to 10 years. The patient died of pneumonia six months after excision, with no recurrence.

Discussion

Neurilemomas manifest as plexiform or multinodular growth patterns are rare. Since Masson's description of two cases, 19 have been added, of which 12 were described in detail (Table 2). The ages of the 18 patients previously reported ranged from 9 years to 71 years, while those of the patients in our series were from 2 to 69, with a mean of 30 years. The duration of symptoms before surgery ranged from one month to 30 years with a mean interval of eight years. Ages at the time of tumour formation, therefore, ranged from 2 years to 58 years, with a mean of 19 years, ranking these tumours as those of children or young adults. Despite the long duration, degenerative changes such as cyst formation or perivascular hyalinization were generally rare, in contrast with ancient neurilemoma (Dahl 1977).

Differentiation from plexiform neurofibroma is important, because the latter has a propensity for malignant transformation (Kleinman et al. 1985; Woodruff et al. 1983). The 23 neurilemomas in the current series showed a multinodular growth, mimicking plexiform neurofibromas. Intraneural growth was evident and immunohistochemical stains for neurofilament disclosed nerve fibers within the nodules, in many cases. In conventional neurilemomas, nerve fibers are usually found around and not within the tumours. Despite the existence of nerve fibers within the current tumours, we consider them to be neurilemomas, because of the general features of encapsulation, combination of Antoni A and B patterns, nuclear palisading with Verocay bodies and proliferation of Schwann cells stained with anti-S-100 protein. The immunohistochemical study also revealed that the tumour cells were weakly reactive to GFAP, as previously reported (Dahl et al. 1982; Memoli et al. 1984), but not reactive to MBP. Immunoreactivities of neoplastic Schwann cells to MBP have been reported both to be positive (Mogollon et al. 1984; Penneys et al. 1984) and negative (Clark et al. 1985).

Concerning the nature of this lesion, traumatic neuroma-like histological patterns pointed out by Reed and Harkin (1983) and a history of antecedent trauma at the tumour sites in two patients (Kleinman et al. 1985: Woodruff et al. 1983) suggest that trauma has a certain role in the formation of this particular variant of neurilemoma. Actually, 14 of the 23 tumours in the current series contained tortuous fascicles of sheath cells often appearing in traumatic neuromas, but there was no history of antecedent trauma at the tumour site in any patient. Any correlation between tumour formation and antecedent trauma remains uncertain.

It is generally considered that plexiform neurilemomas are not associated with von Recklinghausen's disease (Enzinger and Weiss 1983). In our series, however, there were two patients clinically diagnosed as von Recklinghausen's disease. Here, we noted that Masson's first case had a typical syndrome of von Recklinghausen's disease, with multiple cutaneous tumours having the appearance of ordinary neurofibromas. Plexiform neurilemomas, therefore, are not necessarily associated with von Recklinghausen's neurofibromatosis but are occasionally manifest with multiple tumours of the peripheral and central nervous systems. Six of the 20 patients we studied had multiple tumours.

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